Medical Device Quality Systems Manual:

A Small Entity Compliance Guide


(This page last updated: April 14, 1999)

Cover page, Preface, Foreword [Text Format]
Table of Contents [Text Format]

1. The Quality System Regulation [Text Format]
2. Quality Systems [Text Format]
3. Design Controls [Text Format]
4. Process Validation [Text Format]
5. Personnel [Text Format]
7. Equipment and Calibration [Text Format]
8. Device Master Record [Text Format]
10. Purchasing and Acceptance Activities [Text Format]
11. Labeling [Text Format]
13. Packaging [Text Format]
15. Complaints [Text Format]
16. Servicing [Text Format]
17. Quality Systems Audits [Text Format]
18. Factory Inspections [Text Format]
MEDICAL DEVICE QUALITY SYSTEMS MANUAL:
A SMALL ENTITY COMPLIANCE GUIDE

First Edition
(Supersedes the Medical Device Good Manufacturing Practices Manual)

Andrew Lowery, Judy Strojny, and Joseph Puleo
Division of Small Manufacturers Assistance
Office of Health and Industry Programs

CENTER FOR
DEVICES AND
RADIOLOGICAL HEALTH

CDRH

December 1996
(This publication supersedes FDA 91-4179)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOREWORD

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA), develops and implements national programs to protect the public health in the fields of medical devices and radiological health. These programs are intended to assure the safety, effectiveness, and proper labeling of medical devices, to control unnecessary human exposure to potentially hazardous ionizing and non-ionizing radiation, and to assure the safe, efficacious use of such radiation.

The Center publishes the results of its work in scientific journals and in its own technical reports. These reports disseminate results of CDRH and contractor projects. They are sold by the Government Printing Office and/or the National Technical Information Service. Many are available via the FDA home page on the World Wide Web at: http://www.fda.gov.

We welcome your comments and requests for further information.

D. Bruce Burlington, M.D.
Director
Center for Devices and Radiological Health

PREFACE

The Medical Device Amendments of 1976 mandated the establishment of "an identifiable office to provide technical and other nonfinancial assistance to small manufacturers of medical devices to assist them in complying with the requirements of the Federal Food, Drug, and Cosmetic Act." The Division of Small Manufacturers Assistance (DSMA) in the Office of Communication, Education, and Radiation Programs (OCER) was established to meet this requirement. DSMA develops educational materials and sponsors workshops and conferences to provide firms with a firsthand working knowledge of medical device requirements and compliance policies.

This manual covers the Quality System regulation and the basic Good Manufacturing Practices (GMP) requirements that all manufacturers and distributors must consider when they plan to manufacture medical devices, including medical device kits, trays or packs, for distribution in the United States. Model procedures and sample forms are also included in the manual to assist manufacturers.

Adherence to the medical device Quality System regulation makes good business sense and also serves public health aims -- two very good reasons for the Food and Drug Administration (FDA) to encourage compliance. However, a prerequisite to complying with a regulation is a clear understanding of its content. Recognizing this fact, the Division of Small Manufacturers Assistance (DSMA) developed this manual to help manufacturers increase their knowledge of medical device GMP requirements and FDA compliance policies. DSMA also uses this manual at quality system workshops conducted throughout the country.

The Quality System regulation outlines the minimum elements of a system for designing and producing a medical device. Manufacturers of medical devices commonly find
that their quality needs are broader than these basic elements because of the additional need to meet company quality claims as required by paragraph 501(c) of the Federal Food, Drug, and Cosmetic (FD&C) Act and to meet customer needs and requirements.

The DSMA staff and the Office of Compliance (OC) in the Center for Devices and Radiological Health (CDRH) provided valuable assistance in preparing this manual.

For further information, contact the appropriate office within CDRH or call DSMA at 800-638-2041, 301-443-6597 or FAX 301-443-8818. Comments on this manual, related workshops, and other DSMA activities are always welcome.

Lireka P. Joseph, Dr.P.H.
Director
Office of Health and Industry Programs

NOTE TO MANUFACTURERS OF MEDICAL DEVICES

The Quality System (QS) regulation indicates the required end result rather than specifically prescribing how a manufacturer is to comply with this regulation. It is the responsibility of the manufacturer to use good judgment when developing a quality system which appropriately applies the QS regulation to their specific products and operations. The manufacturer, not FDA, bears overall responsibility for the production of high-quality products.

Nevertheless, FDA recognizes that manufacturers may benefit from having guidance, model procedures, and sample forms that others have developed or adopted in an effort to comply with the intent of the regulation. The guidance in this manual includes discussion on the entire QS regulation, plus it provides multiple examples of procedures and forms which can be adopted and modified by manufacturers as appropriate.

We have included a variety of model procedures and sample forms in this manual. However, these are not meant to be official statements of FDA policy. Rather, they represent a compilation of examples that firms may find useful in understanding how some manufacturers have successfully complied with QS and/or GMP requirements. Before any model procedure or form is adopted into a quality system program, the applicability and suitability to a particular device and manufacturing operation should be carefully examined. This manual will assist you in developing a quality system that meets the intent of the FDA Quality System regulation.

FDA also recognizes the continuing need to use innovative approaches, particularly in dealing with small businesses that could be unnecessarily adversely affected by federal regulations. It is hoped that the information in this manual will assist manufacturers in their efforts to establish and maintain a quality system that enhances business. The Office of Compliance at 301- 594-4692 or DSMA at 800-638-2041, FAX 301-443-8818, can be contacted for additional assistance and information.


Sincerely yours,

John F. Stigi
Director
Division of Small Manufacturers Assistance

ABSTRACT

This manual covers requirements of the Quality System regulation that manufacturers of medical devices must consider when they design devices, or when they manufacture, contract manufacture, remanufacture, process, repack, or relabel finished medical devices intended to be commercially distributed. The manual contains articles that explain the various good manufacturing practices (GMP) requirements such as design controls, process validation, calibration, device master records, component control, etc., along with related topics such as labeling. It also contains examples of forms, procedures, decals, etc. Manufacturers may use this guidance when developing their quality system.


This manual is used in the Division of Small Manufacturers Assistance (DSMA) medical device workshops.

The mention of commercial products, their sources, or their use in connection with material reported herein is not to be construed as either an actual or implied endorsement of such products by the Department. The educational information in this manual is not an official statement binding FDA.

Although this guidance document does not create or confer any rights for or on any person and does not operate to bind FDA or the public, it does represent the agency’s current thinking on guidance for quality systems.

Where this document reiterates a requirement imposed by statute or regulation, the force and effect as law of the requirement is not changed in any way by virtue of its inclusion in this document.

Updated 1/1/1997
INTRODUCTION

The current Good Manufacturing Practices (GMP) requirements set forth in the Quality System (QS) regulation are promulgated under section 520 of the Food, Drug and Cosmetic (FD&C) Act. They require that domestic or foreign manufacturers have a quality system for the design and production of medical devices intended for commercial distribution in the United States. The regulation requires that various specifications and controls be established for devices; that devices be designed under a quality system to meet these specifications; that devices be manufactured under a quality system; that finished devices meet these specifications; that devices be correctly installed, checked and serviced; that quality data be analyzed to identify and correct quality problems; and that complaints be processed. Thus, the QS regulation helps assure that medical devices are safe and effective for their intended use. The Food and Drug Administration (FDA) monitors device problem data and inspects the operations and records of device developers and manufacturers to determine compliance with the GMP requirements in the QS regulation.

The QS regulation is in Part 820 of Title 21 of the Code of Federal Regulations (CFR). This regulation covers quality management and organization, device design, buildings, equipment, purchase and
handling of components, production and process controls, packaging and labeling control, device evaluation, distribution, installation, complaint handling, servicing, and records. The preamble describes the public comments received during the development of the QS regulation and describes the FDA Commissioner's resolution of the comments. Thus, the preamble contains valuable insight into the meaning and intent of the QS regulation.

The QS regulation is reprinted in the appendix of this manual.

FLEXIBILITY OF THE GMP

Manufacturers should use good judgment when developing their quality system and apply those sections of the QS regulation that are applicable to their specific products and operations. Section 820.5 of the QS regulation requires that, "Each manufacturer shall establish and maintain a quality system that is appropriate for the specific device(s) designed or manufactured, and that meets the requirements of this part." The word "appropriate" means that the rule is a flexible regulation. However, if manufacturers decide to not implement certain GMP requirements which are qualified by the term "where appropriate," they should document their justification for nonimplementation. The justification should show that not implementing a requirement is not reasonably expected to result in product that does not meet specifications or failure to carry out any necessary corrective action [820.1(a)(30]. Operating within this flexibility, it is the responsibility of each manufacturer to establish requirements for each type or family of devices that will result in devices that are safe and effective, and to establish methods and procedures to design, produce, and distribute devices that meet the quality system requirements. FDA has identified in the QS regulation the essential elements that a quality system shall embody for design, production and distribution, without prescribing specific ways to establish these elements. Because the QS regulation covers a broad spectrum of devices and production processes, it allows some leeway in the details of quality system elements. It is left to manufacturers to determine the necessity for, or extent of some quality elements and to develop and implement specific procedures tailored to their particular processes and devices. For example, if it is impossible to mix up labels at a manufacturer because there is only one label or one product, then there is no necessity for the manufacturer to comply with all of the GMP requirements under device labeling.

The medical device QS regulation requires an "umbrella" quality system intended to cover the design, production, and distribution of all medical devices from simple surgical hand tools to very complex computerized axial tomography (CAT) scanners. It is not practical for a regulation to specify details of quality system elements for such a wide range of products. Rather, the QS regulation specifies general objectives such as use of trained employees, design reviews, design validation, calibrated equipment, process controls, etc., rather than methods, because a specific method would not be appropriate to all operations.

In most cases, it is left to the manufacturer to determine the best methods to attain quality objectives. In some cases, however, the QS regulation does specify the particular type of method to be used, such as written procedures or written instructions. This does not mean, however, that manufacturers cannot vary
from the method specified if the intent of the GMP requirement can be met by another method such as using an engineering drawing plus a model device as manufacturing instructions. Written procedures are not restricted to paper copies. Written procedures may be filed and distributed by automated data processing equipment. This flexibility is allowed by section 820.180.

Typically, large manufacturers will have a quality system that exceeds the medical device QS regulation. Small manufacturers will typically have a proportionally simpler system. FDA recognizes: that a small manufacturer may not need the same amount of documentation that a large manufacturer does in order to achieve a state-of-control; and, that some of records maintained to fulfill the GMP requirements for written procedures may not be as long and complex for a small manufacturer.

After a manufacturer establishes a quality system, it should be maintained. Each manufacturer should assure that with growth and process or product changes their quality system is still adequate. This assurance is obtained through change control, day-to-day observance of operations, and by periodic audits of the quality system. The auditor should first identify the elements of the company's quality system. Next the audit should determine how well each element is functioning, and then determine its adequacy with respect to the intent of the device GMP requirements and meeting the company's quality claims.

MANUAL CONTENTS

To aid auditors, QA managers, and others, this manual provides guidance in the interpretation of the GMP requirements, and demonstrates the flexibility of the QS regulation in its application to diverse devices, manufacturing processes, and manufacturers. In the absence of guidance from FDA, manufacturers may rely on industry, national, and international consensus standards or guidances to meet GMP requirements.

This manual was also developed to aid manufacturers in completing, maintaining, or expanding their quality system. Contents include educational materials, aids, and examples of how to implement elements of a quality system, together with detailed examples of procedures, control forms, and associated data. The examples of typical procedures, drawings, and forms found in this manual were derived from quality systems in the device industry. These materials are not meant to describe universally applicable elements of a quality system that can be used unchanged by any manufacturer. Of course, a form or aid as presented in this manual may be suitable for direct use for a specific device and operation; however, in general, manufacturers will need to use care in adopting and modifying a selected form or procedure to meet the specific quality system needs of their devices and operations.

This manual is arranged as if the reader were starting a new business. That is, as if an entrepreneur were sequentially:

1. obtaining information on GMP requirements;
2. determining the appropriate quality system needed to control the design, production and distribution
of the proposed device;
3. designing products and processes;
4. training employees;
5. acquiring adequate facilities;
6. purchasing and installing processing equipment;
7. drafting the device master record;
8. noting how to change the device master records;
9. procuring components and materials;
10. producing devices;
11. labeling devices;
12. evaluating finished devices;
13. packaging devices;
14. distributing devices;
15. processing complaints and analyzing service and repair data;
16. servicing devices;
17. auditing and correcting deficiencies in the quality system; and,
18. preparing for an FDA inspection.

If manufacturers perform these activities as required by the QS regulation and as expounded in this manual, they should be prepared for a GMP inspection of their operations by an FDA investigator.

Manufacturers and importers of medical devices shall also comply with the Medical Device Reporting (MDR) regulation, 21 CFR Part 803, which requires that serious complaints be reported to FDA. MDR is related to the GMP complaint and failure investigation requirements, which are covered in Chapter 15. If manufacturers comply with the QS regulation and guidance in this manual and in other sources, there is a high probability that they will reduce the frequency of reportable events.

**GMP APPLICATIONS AND EXEMPTIONS**

The QS regulation applies to finished devices intended to be commercially distributed for human use unless there is an approved exemption in effect. GMP exemptions are codified in the classification regulations 21 CFR 862 to 892. The exemption of most Class I devices from design controls is in section 820.30(a).

Certain components such as blood tubing and major diagnostic x-ray components are considered by FDA to be finished devices because they are accessories to finished devices. The manufacturer of such accessories is subject to the QS regulation when the accessory device is labeled and sold separately from the primary device for a health-related purpose to a hospital, physician, or other user.

The designation of a device as a "custom" or "customized" device does not confer a GMP exemption.

Contract manufacturers and specification developers shall comply with the sections of the QS regulation
that apply to the functions they perform.

Contract test laboratories are considered an extension of a manufacturer's quality system and presently are not routinely scheduled for GMP inspections. The finished device manufacturer shall meet the requirement of the QS regulation, particularly 820.50, Purchasing, when they obtain products or services. Internal test laboratories, however, that are part of a corporate manufacturer that provides services to individual corporation factories should meet GMP requirements. Internal laboratories are inspected as part of the FDA GMP inspection of the member factories.

Situations are discussed in the remainder of this chapter where various manufacturers are exempt from the QS regulation or are not routinely inspected. However, these manufacturers are still subject to the FD&C Act. If these manufacturers or any manufacturer render devices unsafe or ineffective, the devices are adulterated and/or misbranded and the manufacturers are subject to the penalties of the FD&C Act.

Exemptions

FDA has determined that certain types of establishments are exempt from GMP requirements; and

FDA has defined GMP responsibilities for others. Exemption from the GMP requirements does not exempt manufacturers of finished devices from keeping complaint files (820.198) or from general requirements concerning records (820.180). Sterile devices are never exempted from GMP requirements. A device that normally would be subject to GMP requirements may be exempt under the following conditions:

- When FDA has issued an exemption order in response to a citizen's petition for exemption,
- When FDA, in the absence of a petition, has exempted the device and published the exemption in the Federal Register,
- When the device is exempted by FDA classification regulations published in the Federal Register and codified in 21 CFR 862 to 892,
- When the device is an investigational intraocular lens (IOL) and meets the requirements of the investigational device exemption (IDE) regulation for IOL's, and
- Through a policy statement, FDA may decide not to apply GMP requirements to some types of devices and processes although the devices may not have been exempted from GMP requirements.

Manufacturers should be aware of the GMP exemption status of their devices. In addition, manufacturers should keep on file records of any specific GMP exemption granted to them by FDA. Upon request during a factory visit, the exemption records need to be shown during normal business hours to the FDA investigator in order to verify that an exemption has been granted.

Component Manufacturers
A "component" is defined by 820.3(c) as "any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device." Component manufacturers are excluded from the QS regulation by 820.1(a)(i). Current FDA policy is to rely upon the finished device manufacturer to assure that components are acceptable for use. Component manufacturers are not routinely scheduled for GMP inspections; however, FDA encourages them to use the QS regulation as guidance for their quality system.

When finished device manufacturers produce components specifically for use in medical devices they produce, whether in the same building or another location, such production of components is considered part of the device manufacturing operations, and the production should comply with the QS regulation.

Accessory devices [807.20(a)(5)] such as hemodialysis tubing or major diagnostic x-ray components, that are packaged, labeled, and distributed separately to a hospital, physician, etc., for health-related purposes are sometimes inappropriately referred to as components. However, FDA considers them finished devices because they are suitable for use or capable of functioning and are distributed for health-related purposes; and the QS regulation applies to their manufacture. Similarly, a device or component including software that is sold as an addition to a finished medical device to augment or supplement its performance is also termed an accessory. An accessory to a medical device is considered a finished device and, therefore, is subject to the QS regulation.

**Remanufacturers**

A remanufacturer is any person who processes, conditions, renovates, repackages restores or does any other act to a finished device which has been previously distributed to significantly change the finished device's performance or safety specifications or intended use from that established by the original finished device manufacturer. Remanufacturers are considered manufacturers. As such, these manufacturers are subject to inspection by FDA and shall meet the applicable requirements of the medical device QS regulation. These manufacturers shall establish and implement quality systems to assure the safety and effectiveness of the devices that are distributed. Such activities include drafting of master records, rebuilding per the master records, inspection and testing, calibration of measurement equipment, control of components, updating of labeling, processing of complaints, and any other GMP requirement applicable to the activities being performed.

Remanufacturers are also required to comply with the labeling requirements of 21 CFR 801.1(c). This labeling regulation requires that where the person or manufacturer named on the label of the device is not the original manufacturer, the name shall be qualified by an appropriate phrase which reveals the connection that person has with the device, e.g., remanufactured by XYZ Company.

**Custom Device Manufacturers**

Section 520(b) of the FD&C Act and the IDE regulation (21 CFR Part 812) define a custom device. Custom devices are exempt from certain statutory requirements. For example, manufacturers of custom
devices are not required to comply with premarket approval requirements (Section 515) and are exempt from premarket notification requirements [Section 510(k)]. Custom devices are NOT exempt from the GMP requirements. Current FDA policy, however, is to not inspect manufacturers of custom devices. Manufacturers of custom devices should comply with the GMP requirements while considering the flexibility allowed.

**Contract Manufacturers**

A person(s) that manufactures a finished device under the terms of a contract with another manufacturer is a contract manufacturer. The agreement between the manufacturers should be documented in a written contract. Contract manufacturers of finished devices shall comply with applicable requirements of the quality system and shall register their establishment with FDA. Depending on the circumstances, both the contractor and manufacturer may be held jointly responsible by FDA for the activities performed.

**Contract Testing Laboratories**

Contract laboratories that designs or test components or finished devices for a manufacturer are considered an extension of the manufacturer's quality system. These laboratories may provide services to a number of customers, many of which are not medical device manufacturers. These contract laboratories are not subject to routine GMP inspections. Through the conduct of quality audits or other means, the finished device manufacturer is responsible for assuring that equipment and procedures used by a lab are adequate and appropriate (820.50). However, an internal test laboratory, if part of a manufacturer that does testing for various facilities within the corporation, is subject to inspection when FDA GMP inspections are conducted at the individual manufacturing facilities. That is, the test laboratory is simply a part of a medical device manufacturer of which all device-related divisions shall comply with the QS regulation.

**Repackagers, Relabelers, and Specification Developers**

Repackaging and relabeling of a device and specification development are defined as manufacturing in 21 CFR Part 807, Establishment Registration and Device Listing for Manufacturers of Devices. Some definitions from 807.3(d) are reprinted below because they affect the applications of the QS regulation.

(d) "Manufacture, preparation, propagating, compounding, assembly, or processing" of a device means the making by chemical, physical, biological, or other procedures of any article that meets the definition of a device in section 201(h) of the Act.

These terms include the following activities:

(1) Repackaging or otherwise changing the container, wrapper, or labeling of any device package in furtherance of the distribution of the device from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer;
(2) Initial distribution of imported devices; or

(3) Initiation of specifications for devices that are manufactured by a second party for subsequent commercial distribution by the person initiating specifications.

As defined above, repackaging and relabeling are manufacturing operations. Further, a repacker, repackager or relabeler is a manufacturer per 820.3(o) and subject to the applicable requirements of the QS regulation. Individuals are repackers or relabelers if they:

- package and/or label previously manufactured finished devices or accessories;

- receive finished devices in bulk (e.g., surgical tubing, syringes, media, etc.,) and repacks them into individual packages and label them;

- receive previously manufactured devices that have been packaged and labeled by another manufacturer, and combine them into a kit with other unpackaged devices which are received in bulk.

Individuals are not considered repackers or relabelers or a manufacturer for purposes of applying the QS regulation if they pack only previously packaged and labeled individual devices into packages for the convenience of the user. (Note that this activity is essentially the same as a drug store employee placing packaged items into a bag labeled with the name of the drug store.)

A distributor who only adds a label bearing their name and address is exempt from the GMP requirements. A manufacturer simply affixing a sticker label bearing the distributor's name and address would not require record keeping demonstrating compliance with labeling controls requirements.

Specification developers provide specifications to contract manufacturers, who produce devices to meet the specifications. The contract manufacturer may package and label the device, or the finished device may be shipped to the specification developer for packaging and labeling.

Specification developers are manufacturers and are subject to the GMP requirements that apply to the activities they conduct, such as various design controls including correct transfer of the design information to a contract manufacturer [820.30(h)]. This activity, in turn, requires an adequate device master record (820.181) and adequate change control [820.40(b)]. Further, if the product carries the specification developer's label, the developer is responsible for maintaining a complaint file and processing complaints, plus maintaining the device specifications and other appropriate documents in the device master record.

**Initial Distributors of Imported Devices**
The initial distributor is the foreign manufacturer's official correspondent with the FDA. With regards to the GMP, this initial distributor is responsible for maintaining complaint files and general record keeping requirements. A procedure shall be established and maintained for receiving, reviewing, and evaluating complaints. All complaints, including oral complaints, are to be processed in a uniform and timely manner. These complaints shall be evaluated to determine whether or not they require reporting to FDA under 21 CFR part 804 or 803, Medical Device Reporting. The initial distributor is also required to evaluate all complaints to determine whether an investigation is necessary, as well as complying with all other requirements in 820.198, Complaint Files. See Chapter 15 in this manual for more complete guidance on handling complaints.

Updated 1/1/1997
INTRODUCTION

The Quality System (QS) regulation requires that each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured (820.5 and 820.20). The GMP requirements are harmonized with the International Organization for Standards (ISO) 9001:1994 and ISO DIS 13485. The quality system should be an integrated effort -- a total systems approach, to satisfy the particular safety and performance needs of a specific manufacturer, product, and user-market. The quality assurance (QA) activities do not simply consist of inspection and testing spot solutions or "fire-fighting," no matter what the product is or how small the manufacturer. In all cases, quality should be considered at the earliest stages in every significant area that has an effect on the quality, safety, and effectiveness of the device. These areas include product development, design verification and validation, component and/or supplier selection, documentation, development of labeling, design transfer, process development and validation, pilot production, routine manufacturing, test/inspection, device history record evaluation, distribution, service or repair, and complaints. Complaints and, of course, favorable comments constitute customer feedback that may result in
improvements in the device, labeling, packaging or quality system.

Most important of all is management commitment. Management and employees should have the correct attitude if their quality system program is to be effective. Quality consciousness should be developed in every employee. Each person should be made aware of the importance of his or her individual contributions in the overall effort to achieve an acceptable level of quality.

After a quality system is in place and checked, it should not be allowed to stagnate -- it should continue to be dynamic. The system remains dynamic through continuous feedback, "big-picture" monitoring by system audits, management review, and corrective and preventive action. Sufficient personnel with necessary education, background, and experience should be in all departments to ensure that quality system activities are properly and adequately performed.

The result is an organization that is operating in a known state-of-control for the device design, process design, manufacturing processes, and records. A properly functioning quality system results in increased safety and effectiveness of the device, reduced liability exposure, reduced regulatory exposure, increased customer satisfaction, less scrap, lower costs, much less confusion, higher employee morale, and, as a result, higher profits.

There are several QA systems in common use, including quality control, good manufacturing practices, product design assurance, the ISO 9000 series of international QA standards, and total quality assurance. Quality control is a minimal system which emphasizes test and inspection. The QS regulation is a government mandated QA system for medical device manufacturers. It emphasizes device, labeling, packaging and process design and all aspects of production: facilities, equipment, design development, design and production documentation, correct design transfer, production control, production records and feedback. Total quality assurance is a system which emphasizes that: all employees and suppliers are responsible for their activities; design requirements are established and met; process requirements are established and met; all production activities are controlled; finished product specifications are met; and feedback results in appropriate corrections.

Product design assurance is a QA system which assures that customer needs are determined, and that product design requirements are established and met. The ISO 9000 series of QA standards ranges from basic quality control to very significant design and production systems.

ISO 9001 is the most comprehensive because it covers design, production, servicing and corrective/preventive activities. The FDA GMP requirements are slightly more extensive because they include extensive coverage of labeling, and complaint handling.

An ideal system for quality assurance is discussed in order to explain the concept of a system. An ideal QA system is composed of an organization that executes a QA program according to documented policy and specifications in order to achieve stated objectives as shown in Figure 2.1.
The written policies and objectives are set by management and are influenced by outside factors such as customer requirements, standards, and regulations. For example, the customer requirements and needs and resulting device specifications should be known to be correct, as these are based on market research, technical and medical considerations, consensus standards, review of existing devices, environmental and compatibility considerations, and design review. The objectives are to produce safe and effective devices at a profit. Ideally, the quality system includes everyone in the company as everyone is fully committed to the quality system program. In addition, however, quality assurance departments such as design QA and production QA are established to help achieve specific objectives. Tasks to be performed to meet these objectives are described in procedures and other documents.

Documentation for a quality system is composed of: product-specific technical documentation such as engineering drawings, component purchase specifications, procedures for manufacturing processes and testing; labels, etc.; and general quality system documentation, such as standard operating procedures (SOPs) for employee training, audits, etc., that are applicable for all products. All activities and product quality are monitored; and any deviations from device and process specifications and company policies are fed back into the system where the deviations are corrected. Likewise, complaint and service information are processed and fed back for appropriate corrections. If the required activities including the feedback are performed, the quality system is self-correcting and, thus, the manufacturer is operating in a state-of-control. FDA requires manufacturers of medical devices to operate in a state-of-control.

**QUALITY SYSTEM PRACTICES**

An adequate and properly implemented quality system such as the one required by the QS regulation or ISO 9001, because of its broad scope, has a high likelihood of preventing the design, manufacture, and shipment of defective products. Basic quality controls such as inspection and testing, are important parts of a quality system because they provide information that should be fed back into the program where action can be taken to correct root causes of quality problems. Identifying and solving quality problems is a core requirement of the QS regulation. This approach is in contrast to merely applying superficial corrections by pass/fail quality-control inspection including rework of finished product or in-process assemblies.
Feedback is necessary to verify the adequacy of the design, manufacturing processes, and the controls used. It also helps trigger corrective action to solve root causes of quality problems rather than just performing rework.

**Design Controls**

Each manufacturer is required by regulation to establish and maintain design control procedures for any class III or class II device, and a selected group of class I devices. The class I devices subject to design controls are devices automated with computer software and the following specific devices:

<table>
<thead>
<tr>
<th>SECTION</th>
<th>DEVICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>868.6810</td>
<td>Catheter, Tracheobronchial Suction</td>
</tr>
<tr>
<td>878.4460</td>
<td>Glove, Surgeon's</td>
</tr>
<tr>
<td>880.6760</td>
<td>Restraint, Protective</td>
</tr>
<tr>
<td>892.5740</td>
<td>Source, Radionuclide Teletherapy</td>
</tr>
</tbody>
</table>

Because the intrinsic quality level of devices and processes is established during the design phase, the quality system program should include this phase if the program is to assure overall quality, meet customer requirements, meet company quality claims, and comply with the intent of the FD&C Act. The terms "product assurance" and "design QA" are often used to identify the quality system activities related to product design. The QS regulation uses the term "design controls." A product assurance system or design QA system combined with a production QA system constitutes a total quality system.

Quality system, production, regulatory, and other appropriate personnel should participate in the review, evaluation, and documentation of the components, device, and process design. It is from data established during this preproduction phase that all other activities derive such as, purchasing, processing, and testing. Development and validation data are also useful in cases of regulatory or product liability actions to show that the design and manufacturing processes were well conceived and properly validated, reviewed, and documented.

Total quality systems extend from customer requirements through development and production to customer use and feedback. Thus total quality systems encompass the medical device law and regulations, particularly the QS regulation. The FD&C Act, and its implementing regulations such as those for Labeling, Premarket Notification, Investigational Device Exemptions (IDE), Premarket Approval (PMA), and GMP requirements impact the quality of devices at various times during the design product life-cycle. The IDE, PMA, 510(k), labeling and QS regulation with their preproduction and production requirements constitute a total quality system. For example, Section 501(c) of the Act states that a product is adulterated if it does not have a quality equal to the quality stated or implied by the product labeling. Analysis of device recall problem data by FDA has shown that such problems are
divided almost equally between design and production. Thus, a production quality assurance program is not sufficient to produce safe and effective devices -- design shall also be covered. A design quality assurance system is required by the QS regulation.

Two other reasons for having a total quality system are 21 CFR Part 803, Medical Device Reporting (MDR), and product liability. MDR requires manufacturers of medical devices to report to FDA certain adverse events that they receive from any source. Product liability actions are often the result of poor design, labeling, and manufacturing. Reporting and liability exposure are reduced by using a total quality system.

Intrinsic or desired quality is established by the design specifications for the product, its components, and the manufacturing processes. Complying with the QS regulation assures that the manufacturing processes can consistently achieve desired levels of quality and that the finished device meets its device master record specifications. This result is a significant quality step. However, if the device as designed is of poor quality, the GMP production controls will only assure that a poor quality device is manufactured. Thus, the QS regulation requires an overall quality system program, which embraces evaluation of customer needs; product design; verification and validation; labeling development and control; all manufacturing and control activities; and customer feedback.

Component Selection

Component and raw material specifications developed during the design phase should be well conceived and adequate for their intended purpose. New components or components for an unusual application need to be verified (qualified) for the intended use. In some cases, where large quantities of components or raw materials are involved, the specifications should include valid and well understood methods of sampling and acceptance. These specification and sampling/acceptance plans should also be accessible and acceptable to suppliers. The specifications are device master record (DMR) spec document or the specifications appear in a DMR drawing or procedure.

Manufacturers shall establish and maintain procedures to ensure their purchased and otherwise received products and services conform to their specified requirements. The manufacturers shall then assess their suppliers, contractors, and consultants based on their ability to meet the established specifications. When possible, an agreement shall be established to include that the suppliers, contractors, and consultants will notify the manufacturer of any changes in the product or service that may affect the quality of a finished device.

Labeling Content

The regulations in 21 CFR Part 801, Labeling; Part 809, In Vitro Diagnostic Products for Human Use; and Part 812, Investigational Device Exemptions, are intended to control the content of labeling. Likewise, 21 CFR Part 807, Premarket Notification; and Part 814, Premarket Approval and 820.30, Design Controls, help control the content of labeling by design and premarket submissions. The intent of
these regulations and the FD&C Act is for manufacturers to have a labeling control program such that their labeling always complies with the regulations and meets the needs of the users. By a formal process under a total quality system during the design phase, clear and concise printed and/or software labeling are written and reviewed; and the ink substrate and attachment methods for printed labeling are developed. Such labeling is designed to meet customer and regulatory requirements. Thereafter, the procurement, use of the correct label, and the correct attachment of labels is assured under a manufacturer's quality system elements for these activities.

**Process Quality**

Manufacturing methods and processes to be used should be developed, equipment selected, and processes and methods qualified. For all significant processes such as welding, molding, lyophilizing, sterilizing, and packaging/sealing where the output cannot be fully verified, the qualification should include a full validation of the processes. The output may not be fully verified for economic, technical, or practical reasons and thus validation is needed. Production specifications and methods employed in manufacturing should result in standard in-process and finished products without excessive sorting or reprocessing. Inspection and test methods should be developed that will adequately monitor product characteristics to make certain these are within the acceptable specifications. These methods should be developed, evaluated, validated where necessary, and documented during the product and process development phase. The methods should be implemented at the beginning of routine production.

Any adverse effects the manufacturing processes, manufacturing materials, or equipment may have on device safety and performance should be identified. Where necessary, procedures have to be developed, implemented, and monitored to control these characteristics. Quality system personnel should participate in the timely (i.e., early) development of special controls, test or inspection methods, or training programs needed to insure product quality. Acceptance methods should be developed for accurate measurement of outgoing product quality.

**Management Responsibility**

As set forth by the QS regulation (820.20), one of the most important responsibilities of management when developing a quality system is to establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization. This means each manufacturer shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks. The QS regulation also requires that each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the GMP requirements. To meet these regulatory requirements, manufacturers are required to provide adequate resources, including the assignment of trained personnel for management, performance of work, and assessment activities, including internal quality audits.
Management with executive responsibility shall appoint a member of management who will have authority over and responsibility for:

- Ensuring that quality system requirements are effectively established and effectively maintained; and
- Reporting the performance of the quality system to management with executive responsibility for review.

Thus, the QS regulation requires that management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the regulatory requirements and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews shall be documented.

The quality assurance personnel should be able to identify system problems, to recommend and provide solutions, and to verify implementation of the solutions. Other personnel may also identify and solve quality problems. The quality system should support such activities by all personnel. Feedback from quality assessment activities is necessary to verify the adequacy of the manufacturing process and the controls used. It also helps trigger corrective action to solve root causes of quality problems rather than just performing rework.

Typically, a quality system identifies problems with device quality through review of verification and validation data, inspection/test data, analysis of device history and service records, failure analysis, analysis of complaints, and review of other objective data. In this regard, reduction in productivity is often an indicator of quality problems. Low morale and confusion are indicators of inadequate procedures, and/or training and poor management. Also, measurement of scrap and rework is an effective method of detecting quality problems and reducing costs. These are examples of sources that provide feedback to the quality system.

In conclusion, each manufacturer is required to establish a quality plan which defines the quality practices, resources, and activities relevant to the devices that are designed and manufactured. The manufacturer shall establish how the requirements for quality will be met [820.20(d)]. Each manufacturer shall establish quality system procedures and instructions. To facilitate the understanding, use, review, and updating of the quality system, an outline of the structure of the documentation used in the quality system shall be established where appropriate [820.20(e)].

**Formal and Documented Quality System**

The QS regulation requires that each manufacturer prepare and implement quality system procedures adequate to assure that a formally established and documented quality system is implemented. The system should include not only formal documentation, but also an obvious commitment to quality from top management. There should be manifest indications that management recognizes the need for a
quality system in order to assure quality products. In many manufacturers, this commitment is accomplished through means such as: a management policy; assignment of responsibilities and authorities; and general statements and actions such as employee training that define goals of the quality system. This policy is supported by a number of more detailed quality system documents such as verification methods, sampling procedures, inspection/test procedures, product audits, and records indicating that measurement and monitoring of quality has occurred. The number of documents needed depends on the size and complexity of the operation and the characteristics of the product. The QS regulation requires the manufacturer to maintain various records such as:

- design history files,
- device master records,
- device history records,
- maintenance schedules and records,
- complaint files and failed device/component files,
- audit reports,
- distribution records, and
- personnel training records.

Most of these records are discussed in more detail in later chapters. In each case, the records should be appropriate for the device and the operation involved. Any changes to device master records should be made by a formal procedure and be formally approved.

Among other records, the device master record contains manufacturing procedures and standard operating procedures (SOP's). Some manufacturers tend to write an excessive number of general SOP's. Manufacturers should not generate and use procedures that are not needed. Also, standard operating procedures tend to not match actual operations because the operations gradually change as the company grows or as products are added without amending the procedures. Such procedures may require operations that have no benefit, or require excessive collection of data, or collection of data that is never used. Thus, manufacturers need to occasionally flow chart and analyze their operations to determine, among other things, if the existing procedures are inadequate, correct, or excessive. Flow-charting is a tool that directs a detailed audit of an operation. Flow-charting to analyze operations is an excellent method for improving operations and the associated quality system activities. At the end of Chapter 10, Purchasing and Acceptance Activities, an example of a flow-chart is contained in PA-1004, Procedure for Receiving and Inspection of Material, integral page 4 of 9.

Approval of Product

The quality system includes procedures for assuring that all products such as components, packaging, labeling, manufacturing materials, and finished devices have been approved for use; and that contracted items and services are suitable [820.50, 820.80]. Likewise, the quality system shall assure that rejected items are identified and properly disposed [820.90]. Additionally, the quality system shall assure that production records are reviewed before the product is distributed [820.80(d)]. These records are part of
the device history record. Device history records shall be reviewed to verify that the operations represented have been properly conducted and that the records are complete.

**Quality Acceptance Activities**

The quality system shall determine that all tests and inspections are performed correctly (see 820.80, 820.181, and 820.20). Some of the methods used to accomplish this are adequate test and inspection procedures, training of test personnel, quality system audits, review of quality system records, and product audits. However, simply instituting a quality system and checking that it is conducted correctly is not enough to satisfy the QS regulation. The regulation also requires that the quality system be appropriate and adequate for the purpose. This determination should be done during final product development, pilot production, and, of course, whenever product and/or processes are modified. In cases where conformance to specifications cannot be adequately measured by in-process or finished product testing and inspection, the system should include validation of processes.

**Quality System Audits**

The QS regulation requires (820.20) that each manufacturer shall prepare and implement quality system procedures adequate to assure that a formally established and documented quality system program is performed. Many activities are required to fulfill this requirement. As management performs their assigned routine duties, they should be aware of the obvious aspects of the quality system. However, to make sure that all aspects, obvious, hidden or subtle, of the required program exist and are operating correctly, the QS regulation requires planned and periodic audits (820.22) of the quality system. Management with executive responsibility reviews audit reports as part of their review of the suitability and effectiveness of the quality system.

**Employee Training**

QS regulation requires quality awareness training for manufacturing and quality system personnel [820.25(b)]. Personnel involved in quality system activities shall be properly trained, both by education and experience. No matter how effective quality system and production systems are as concepts, people still play the major role in producing a quality product. Lack of training -- as reflected in instances of negligence, poor operating techniques, or inability of employees to discharge their functions properly -- can lead to defective products and, sometimes, to regulatory or liability problems. Management should be diligent in looking for factors that indicate a need for employee training.

A quality system should include an ongoing formal program for training and motivating all personnel. All employees should be made aware that product quality is not solely the responsibility of management. Quality is the responsibility of every employee -- any employee can potentially generate a quality problem through negligence. It is extremely important to understand the following points with respect to typical quality-related functions.
• Top management sets the quality attitude for the company.

• Research and development has primary responsibility for designing quality into the device.

• Technical services or an equivalent functional group has primary responsibility for documenting the design.

• Manufacturing, process or "scale-up" engineering has primary responsibility for designing quality into the manufacturing processes.

• Manufacturing personnel have primary responsibility for producing devices that have the maximum level of quality that can be achieved based on the product and process designs.

• Quality system personnel have primary responsibility for the program's management, status reports, audits, problem identification, data analysis, etc., as described in the QS regulation and in this manual.

A medical device manufacturer should NEVER try to operate on the basis that only the quality system organization has primary and direct responsibility for the quality of the products. To do so means that quality problems will not be solved in a timely manner because attention is directed toward the wrong organization. In reality, it is part of the responsibility of the quality system to see that attention is directed toward the correct department if a quality problem arises.

Where necessary, employees should be certified to perform certain manufacturing or quality system procedures. Records of training and/or certification shall be maintained. Personnel performing quality system functions should:

• have sufficient, well-defined responsibilities and authority;
• be afforded the organizational freedom to identify and evaluate quality problems;
• be able to formulate, obtain, and recommend possible solutions for quality system problems; and,
• verify implementation of solutions to quality problems.

QUALITY SYSTEM MAINTENANCE

After the quality system is operational, personnel should continue to look for problem areas or factors that can have an impact on product quality. Many factors that can have an impact on product quality include:

• changes in, or absence of, personnel;
• uncomfortable working conditions (e.g., breakdowns in air conditioning);
• increases in workload or production rates;
• introduction of new production or inspection equipment;

● changes in company incentive techniques (e.g., placing hourly employees on piecework can cause deterioration of product quality); and
● changes in sources for purchased components and materials, as well as changes in components, devices, or process techniques.

As noted, quality system audits and flow-charting of operations are excellent methods for determining the detailed status of the system. Correcting problems or responding to conditions identified by audits, operational analyses, and customer feedback data can result in quality system improvements.

MEDICAL DEVICE REPORTING

FDA has promulgated regulations [803] for manufacturers, distributors, and initial distributor(s) requiring them to establish and maintain reports, including the Medical Device Reporting (MDR) reports for serious injuries, death, or certain other adverse incidents. If a manufacturer has a quality system as required by the QS regulation, the frequency of MDR reporting should be minimized.

Updated 1/1/1997
3. Design Controls

Introduction
Coverage
QUALITY SYSTEM
Personnel Training
DESIGN AND DEVELOPMENT PLANNING
Interface
Structure of Plans
DESIGN INPUT
Input Checklists
DESIGN REVIEW
Combination Devices
Preparation For Reviews
Why Design Reviews
Types Of Design Review Meetings
Design Review Requirements
End Of Initial Design
DESIGN OUTPUT
Documenting Design Output
Acceptance Criteria
Design Output Approval
DESIGN VERIFICATION AND VALIDATION
Design Evaluation versus Specifications
Software Validation
Labeling Verification
DESIGN TRANSFER
DESIGN CHANGES
DESIGN HISTORY FILE
EXHIBITS
Design Input Requirements Procedure
INTRODUCTION

The Safe Medical Devices Act of 1990 added design validation requirements to the GMP requirements in section 520(f) of The Act. Section 820.30 of the Quality System (QS) regulation lists the design control requirements that manufacturers should satisfy to be in compliance. This chapter describes design controls and provides guidance to assist manufacturers in complying with design control requirements.

"Design Control Guidance for Medical Device Manufacturers" is another document that may assist manufacturers in understanding the intent of the design control requirements. This manual interprets the language of the QS regulation and explains the underlying concepts in practical terms. "Do It By Design: An Introduction to Human Factors in Medical Devices" is a document that contains background information about human factors as a discipline, describes and illustrates device problems and discusses human factors principles and methods as a part of the design control system. Both of these manuals are possible resources for manufacturers who are either developing or improving their design control system. These manuals are also available through DSMA.

Coverage

The design controls section 820.30 of the QS regulation applies to the design of products, and processes and changes to existing designs and processes. Changes to existing designs should be made in accordance with design control requirement even if the original design was not subject to these requirements. Design controls are not retroactive to completed portions of ongoing design programs.

Each manufacturer of any class III or class II device, and class I devices automated with computer software and those listed below shall establish and maintain procedures to control the design of the device in order to make certain that specified design requirements are met. Manufacturers of other Class I devices should develop and document their devices under their own design control system because the documentation is needed to help meet the device master record requirements in 820.181 and marketing submission requirements. Thus, manufacturers of exempt Class I devices are encouraged to use 820.30, Design Controls, as guidance.

<table>
<thead>
<tr>
<th>Classification Section</th>
<th>Class I Devices Subject to Design Controls Listed in Paragraph 820.30(a)(2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>868.6810</td>
<td>Catheter, Tracheobronchial Suction</td>
</tr>
<tr>
<td>878.4460</td>
<td>Glove, Surgeon's</td>
</tr>
<tr>
<td>880.6760</td>
<td>Restraint, Protective</td>
</tr>
<tr>
<td>892.5740</td>
<td>Source, Radionuclide Teletherapy</td>
</tr>
<tr>
<td>All Sect.</td>
<td>Devices automated with computer software</td>
</tr>
</tbody>
</table>
The design requirements for the device are primarily specified by the manufacturer; however, FDA has a few design requirements in the 21 CFR Part 801 labeling regulations and in Parts 1000-1050 which cover radiological and electronic products. A few of the FDA design requirements are in standards. For example, some parameters for medical gloves are in standards by the American Society for Testing and Materials (ASTM). (That is, medical gloves are required to meet these standards in order to be substantially equivalent to gloves already in commercial distribution.)

QUALITY SYSTEM

Each manufacturer is required to establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured [820.5 and 820.1(a)(3)], and that meets the requirements of Part 820. Therefore, the details of design control systems will vary depending on the complexity of the product or process being designed. However, all non-exempt manufacturers including very small manufacturers and manufacturers that design less complex devices or processes are expected to define, document and implement design control procedures and other quality system procedures as called for in the regulation. One of these, a sample design input procedure, is exhibited at the end of this chapter.

Manufacturers may establish one design control procedure to cover the various design control sections in 820.30; or, they may use one or more procedures for each topic. Multiple procedures may be easier to develop, update and implement. Medium to large manufacturers may have several additional procedures to support their main design control procedures. Design control procedures may be part of the quality system records (QSR) noted in section 820.186.

Personnel Training

Personnel training in 820.25 is one of the quality system requirements, which applies to employees that perform any activity covered by the QS regulation including all design activities.

Manufacturers are required to establish procedures for identifying training needs and making certain that all personnel are trained to adequately perform their assigned responsibilities. Design personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. In particular, personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.

Most technical employees need various degrees of training, as appropriate, in the medical device regulations, safety, labeling, human factors, verification, validation, design review techniques, etc.

DESIGN AND DEVELOPMENT PLANNING

Developing a new device and introducing it into production are very complex tasks. For many new devices and associated manufacturing processes that use software, these tasks are further complicated because of the importance of software, and the possibility of subtle software errors. Without thorough planning, program control, and design reviews, these tasks are virtually impossible to accomplish without
errors or leaving important aspects undone. The planning exercise and execution of the plans are complex because of the many areas and activities that should be covered. Some of the key activities are:

- determining and meeting the user/patients requirements;
- meeting regulations and standards;
- developing specifications for the device;
- developing, selecting and evaluating components and suppliers;
- developing and approving labels and user instructions;
- developing packaging;
- developing specifications for manufacturing processes;
- verifying safety and performance of prototype and final devices;
- verifying compatibility with the environment and other devices;
- developing manufacturing facilities and utilities;
- developing and validating manufacturing processes;
- training employees;
- documenting the details of the device design and processes; and,
- if applicable, developing a service program.

To support thorough planning, the QS regulation requires each manufacturer to establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation.

The plans should be consistent with the remainder of the design controls. For example, the design controls section of the quality system requires a design history file (DHF) [820.30(j)] that contains or references the records necessary to demonstrate that the design was developed in accordance with the:

1. approved design plan, and
2. regulatory requirements.

Thus, the design control plans should agree with, and require meeting, the quality system design control requirements. One of the first elements in each design plan should be how you plan to meet each of the design control requirements for the specific design you plan to develop; that is, the design plans should support all of the required design control activities. Such plans may reference the quality system procedures for design controls in order to reduce the amount of writing and to assure agreement.

Interface

Design And Development Planning section 820.30(b) states:

"The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process..."
If a specific design requires support by contractors such as developing molds, performing a special verification test, clinical trials, etc., then such activities should be included or referenced in the plan and proactively implemented in order to meet the interface and general quality system requirements. Of course, the interface and general requirements also apply to needed interaction with manufacturing, marketing, quality assurance, servicing or other internal functions.

Proactive interface is an important aspect of concurrent engineering. Concurrent engineering is the process of concurrently, to the maximum feasible extent, developing the product and the manufacturing processes. This valuable technique for reducing problems, cost reduction and time saving cannot work without proactive interface between all involved parties throughout all stages of the development and initial production program.

**Structure of Plans**

Each design control plan should be broad and complete rather than detailed and complete. The plan should include all major activities and assignments such as responsibility for developing and verifying the power supplies rather than detailing responsibility for selecting the power cords, fuseholders and transformers. Broad plans are:

- easier to follow;
- contain less errors;
- have better agreement with the actual activities; and
- will require less updating than detailed plans.

Over the years, several manufacturers have failed to follow this advice and opted for writing detailed design control procedures. They reported being unable to finish writing the over-detailed procedures and were unable to implement them.

Regardless of the effort in developing plans, they usually need updating as the development activities dictate. Thus, the QS regulation requires in 820.30(a) that the plans shall be reviewed, updated, and approved as the design and development evolves. The details of updating are left to the manufacturer; however, the design review meetings are a good time and place to consider, discuss and review changes that may need to be made in the design development plan.

**DESIGN INPUT**

Design input means the physical and performance requirements of a device that are used as a basis for device design [820.3(f)].

Section 820.30(c) Design Input, requires that each manufacturer shall establish and maintain procedures to make certain that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. Also, a design requirement in 820.130
requires that each manufacturer shall make certain that device packaging and shipping containers are
designed and constructed to protect the device from alteration or damage during the customary conditions
of processing, storage, handling, and distribution. The intent of 820.130 is to add the broad conditions that
are considered for a packaging design. Packaging design activities should be done according to design
controls. Likewise, the design of the content and physical parameters of labeling are covered by design
controls. Manufacturers that are exempt from design controls shall labeling and packaging specifications
in the DMR (820.181) and are encouraged to use the QS design controls as guidance.

The input procedures shall address incomplete, ambiguous, or conflicting requirements. The design input
requirements shall be documented and shall be reviewed and approved by a designated individual(s). The
approval, including the date and signature of the individual(s) approving the requirements, shall be
documented.

Under a design control system, manufacturers should identify device requirements during the design input
phase or beginning of the design activity. Design input includes determining customer needs, expectations
and requirements plus determining regulatory, standards, and other appropriate requirements. These
various requirements are documented by the manufacturer in a set of device requirements. A set of design
input requirements, when converted to engineering terminology, finalized and accepted as part of the
device master record is called a device or product specification.

The design input phase usually is a continuum because intensive and formal input requirements activities
usually occur near the beginning of the feasibility phase and continue to the early physical design
activities. After the initial design input phase there are also intensive and formal activities to reduce the
input requirements to engineering-type input specifications -- usually called a product or device
specification.

At the opposite end of the design program, the last event is initial production which may be pilot
production or the beginning of routine production. Whether a manufacturer starts with pilot or routine
production depends on the nature of the new device and associated production. Pilot devices may be
distributed after design validation of initial units is completed if they meet all of the device master record
and other GMP requirements. Some manufacturers, however, use the pilot models in training programs
for technical writers, production and service personnel, etc. Pilot models are also commonly used in early
marketing displays.

After the concept of the new device design is established, the following basic design input questions
should have been answered:

1. What is the real need for the new device?

2. Where will the new device be used?

3. Who will use the new device?
4. How will the new device be used?

5. With what devices will the new device be used?

6. How long will the new device be used? and

7. Other questions related to the specific device to be developed.

Designing a device and verifying that it meets customer requirements are expensive and time consuming activities. Therefore, to control these activities and increase the probability of achieving desired safety and performance characteristics, device, software, and process requirements and specifications should be thoroughly reviewed and approved before physical design and development begins. As the design evolves, the hardware, software, packaging, labeling, etc., shall be verified [820.30(f)] and reviewed [820.30(e)] versus their latest specifications to verify that design input requirements have been met.

**Input Checklists**

Device requirements should identify all of the desired performance, physical, safety and compatibility characteristics of the proposed device and, ultimately, the finished device. Design input also includes requirements for labeling, packaging, manufacturing, installation, maintenance and servicing. The final device specifications should cover ALL of the device characteristics. The device specifications may incorporate other specifications by reference such as reference to the manufacturer's list of specifications for a type of device, to specific paragraphs in standards, or to all of a standard, etc. with respect to a referenced specification. It should be very clear exactly what is going to be met. A failure to properly address characteristics or factors such as immunity from transients in the power source, thermal stress, electromagnetic compatibility (EMC), packaging protection, shipping stability, proper maintenance, etc., can have disastrous consequences.

It is possible to diligently develop device requirements and still forget one or more elements in the final specification. Hopefully, no key factors will be left out. To reduce the probability of a requirement or characteristic being left out, a specification checklist(s) may be used during the design input phase. A checklist should be developed that is broad based but also germane to the product line of the manufacturer. If used, a checklist should be part of a standard operating procedure such as a Design Input Specification Procedure.

The input requirements should cover any standards that the manufacturer plans for the device to meet. In the United States, information about essentially all national and international standards may be obtained from the American National Standards Association (ANSI), 11 West 42nd Street, New York, New York, 10036, phone 212-642-4900. ANSI is a private organization, which monitors most of the standards activity in the United States and foreign activity in which U.S. citizens "officially" participate. Thus, ANSI can supply addresses and other information about all well established standards writing groups. Also, ANSI has for sale many different types of standards including quality system standards. For example, the International Electrotech Commission has a draft design review standard, "Guide on Formal
Design Review" (plus a supplement), which should be helpful to product assurance/design control personnel.

The QS regulation requires that the input procedures shall address incomplete, ambiguous, or conflicting requirements. Thus, every reasonable effort should be made to collect all of the requirements from which the designers can generate detailed design specifications that are clear, correct and complete.

At the end of the major aspects of the design input stage, the design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

A documented device specification or set of specifications derived from the input requirements should exist at the beginning of the physical design project. The device and other related specifications should be kept current as the design of the device, packaging, labeling and manufacturing processes evolve during the development program. As the physical design evolves, the specifications usually become more specific and more detailed.

The device specification will undergo changes and reviews as the device design evolves. However, one goal of market research and initial design reviews is to establish complete device requirements and specifications that will minimize subsequent changes.

Old versions of the input requirements and later the input specifications are put in the design history file (DHF) or indexed in the computer as part of the DHF to help show that the design plan was followed.

**DESIGN REVIEW**

Design review [820.30(e)] is one of the key design control elements in a quality system. The objectives of design review are stated in the definition of design review in 820.3(h) as follows:

Design review means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

To meet the systematic design review requirement, device design and design reviews should progress through defined and planned phases starting with the design input phase and continuing through validation of initial production units or lots. Subsequent activities are usually design changes.

To meet the design review comprehensive requirement, assessments should include a formal review of the main device and subsystems, including accessories, components, software, labeling, and packaging; production and resource needs; and installation and service, if needed. The scope includes performance, physical safety, compatibility with other devices, overall device system requirements, human factors, and environmental compatibility.
Even though users or medical practitioners will be aware of direct medical requirements, they may not be fully aware of physical safety, compatibility, system, human factors, and environmental requirements. Thus, the reviews of the design input and the design should extend beyond merely satisfying user-stated requirements in order to assure that safety and effectiveness goals are met.

As the development program progresses, the reviews should cover producibility and production documentation such as assembly drawings, manufacturing instructions, test specifications, test procedures, etc.

The extent and frequency of design reviews depends on the complexity and significance of the device being evaluated.

When the design program is a redesign of an existing device, a special effort should be made to assure that data obtained from previous failures, complaints, and service records are made available and reviewed by those responsible for design, design input and design review.

Combination Devices

Marketing submissions to FDA for drug delivery, drug coated, etc., devices are required to have appropriate data that supports combination claims. The verification of combination devices requires interaction between device, drug or other manufacturers. Records of this interaction, such as design review meeting minutes, are required in order to meet the interface requirements of 820.30(b), Design and Development Planning. The labeling and particularly the cross-labeling of combination devices should be carefully analyzed during verification and validation activities, and design review meetings.

Preparation For Reviews

The designated moderator or other designated employee should announce the formal review meetings with appropriate lead time and include an agenda.

Persons who are making presentations should prepare and distribute information to help clarify review issues and help expedite the review. However, the intent of the quality system is not that presentations be so formal and elaborate that designers are spending excessive time on presentations rather than on designing a safe and effective device.

Persons who plan to attend a review meeting should come prepared to discuss the key issues on the agenda and issues related to the current design phase. Design review meetings are a great educational forum. However, design review meetings should not be used as a primary tool to educate or bring new employees or unprepared employees up-to-speed. To do so detracts from the intent of the meeting and detracts from the intent of the GMP requirements. Obviously, design review is also an excellent educational tool. However, new, or new-to-the-project employees should be primarily oriented by other means that do not detract from the primary function of design review meetings.
Why Design Reviews

Design reviews are conducted for design definition, selection and adequacy; communication; and resolution of problems and issues. For example, the design review of the design input requirements and subsequent design input specifications for the device, labeling, packaging and accessories is performed to help select the best and/or needed characteristics and requirements, usually from among many available and sometimes conflicting inputs.

The design review of the initial requirements allows input from all parties. Various people may participate and "buy in" or "become part of the program." As the design input and review activities progress, any conflicts are resolved and the preliminary specifications for the device, accessories, labeling, and packaging are established. Herein, the device, accessories, labeling and packaging is called the device system. Because of the establishment of these input requirements and subsequent specifications, plus interface and communication during the reviews, all personnel are directed toward the goal of developing the "exact" same device system.

As the development progresses and the design and production processes evolve, design reviews reduce errors, help avoid problems, help find existing problems, help propose solutions, increase producibility and reduce production transfer problems. The relentless inquiry during design reviews will expose needed design input requirements and/or design corrections that otherwise may have been overlooked.

Throughout the design program and particularly toward the end of the development cycle, design reviews help assure that the final design of the device system meets the current design requirements and specifications.

Types Of Design Review Meetings

Design review meetings may be grouped into two levels such as:

- total or major program review meetings, and
- sub-program or team review meetings.

Some of the review meetings need to be total or major program review meetings because this is the only type of review meeting that will satisfy all of the GMP review requirements, particularly the interface requirement for interaction between or among different organizational groups. However, sub-program, team and contractor review meetings are design review meetings, are subject to quality system design controls, and should be conducted in a manner that meets the GMP requirements. Sub-program or team meetings are encouraged as these can be very effective and efficient in reviewing and resolving sub-program issues.

The records of total program and team meetings are part of the device design history file. The team review records or a summary of team records and the current design documentation are to be available, as
appropriate, at total program review meetings.

Design review meetings are called under two scenarios:

- first are the meetings that are preplanned and called at least on a per design phase;
- second are ad hoc meetings that are covered in the broad plans and are called to review or resolve a specific problem or issue.

The preplanned design review meetings and ad hoc meetings are part of the planning and interaction that are required in 820.30(b), Design and Development Planning. That is, the manufacturer should expect, plan for, and encourage appropriate ad hoc meetings as well as the major design review meetings. Reasonable notes and copies of significant engineering documents discussed during total device system, ad hoc, contractor, and other review meetings are part of the device design history file.

**Design Review Requirements**

The objectives of design review are stated in the definition noted above. How these objectives are to be achieved are presented in the design review requirements. The main design review requirements are in 820.30(e) of the QS regulation as follows:

Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file.

There are four requirements related to design reviews:

1. The meetings should be formal. That is, key attendees are designated and the meetings are conducted at least once per stage/phase, are planned, are announced or are periodic, have an appropriate agenda, notes are recorded, etc., according to the manufacturer procedure for design reviews.

The design review procedure should be broad and complete in that it contains information about all of the requirements. However, the procedure should not be so detailed that it cannot be followed. Over the years, several manufacturers have failed to follow this advice, tried to write detailed design QA procedures, and have reported that they were unable to finish writing the over-detailed procedures and were unable to implement them.

2. To meet the definition of design review in 820.3(h), the review should include persons who are intimately knowledgeable about the technical characteristics of the design such as performance, safety,
compatibility, etc. In many manufacturers this can only be done by those persons responsible for the design. However, reviews are to be objective, unbiased examinations by appropriately trained personnel which should include an individual(s) not responsible for the design. The moderator of the review meeting may be one of the persons not responsible for the design.

To meet interface and other review requirements, the review meetings should, as appropriate, include representatives of R&D, Engineering, Technical Support Services, Production Engineering, Manufacturing, Quality Assurance, Marketing, Installation and Servicing, Purchasing and contractors. Design review should, as applicable and at the appropriate phase, include those responsible for coordinating or managing preclinical and clinical studies.

3. Pre- and post-review meeting significant responsibilities and assignments should be documented [820.30(b)]. These assignments are not unusual -- they are simply ordinary work required to develop a new product or modify an existing product. The progress and/or results of such assignments would typically be reported at the next review meeting. Documentation is not required for detailed day-to-day development activities that are part of the designers routine job.

4. The design review meeting results are made a part of the device design history file. The results should include minutes and should include notes, or annotated draft drawings and annotated draft procedures that played a significant role during the design review. Such documents help show that plans were followed, verification/validation was reviewed, and, to some extent, how the design evolved.

The QS regulation does not require that every document mentioned, referenced or used during a design review be placed in the design history file.

The device design review meeting minutes should include information such as:

- moderator and attendees,
- date and design phase/stage,
- plans and/or agenda,
- problems and/or issues to identify and solve,
- minutes and reports, and
- follow-up report(s) of solutions and/or the next review covers the solutions and remaining issues.

Manufacturers may use a form to capture some of this information for minutes such the device, date, moderator, attendees, major phase, problems, assignments, etc. The device design review minutes are a key and required part of the design history file. The minutes also help consolidate development information and the current minutes are also a brief record of some of the immediate development tasks to be done.

**End Of Initial Design**

The design control requirements, particularly design validation, give clear insight into when the initial
design effort is completed. The end of the total design effort has not been reached until it is known that the initial production devices, when transferred to production and produced per the device master record, meet all of the current design specifications. This fact can only be determined by performing design validation on one or more samples of the finished production units as required by 820.30(g). Initial production and subsequent validation are well defined stages; and, therefore, design review(s) shall be performed as required by 820.30(e), Design Review.

Thus the design validation of initial production should be followed by a "final" design review to meet the design review requirement. If the validation of the final design and subsequent design review(s) reveal design problems, then design changes are required to correct these problems. Design changes require another design verification and, where appropriate, validation and review of all parts or the affected parts of the device system.

**DESIGN OUTPUT**

Design output per 820.3(g) means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.

Device master record (DMR) means a compilation of records containing the procedures and specifications for a finished device.

The design output at each phase are documents and physical design elements that are either complete or are used to move the design effort into the next phase. For example, the first design output will usually be the design requirements document. From the requirements and their engineering knowledge, the designers will derive the preliminary design specifications. Then the physical design begins. For example, the designers may begin the selection of known routine components that are part of the design and begin documenting their purchasing and acceptance requirements documented to meet 820.50 Purchasing Controls, (b) Purchasing Data which requires that each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services.

Other components will be selected as the design evolves. The design output for some special or new components, or components in unusual applications, will include verification protocols, purchasing and acceptance requirements.

Many of the design output documents are documents that directly form part of the DMR. The remaining DMR documents are created by quality assurance, production engineering, process engineering, technical writing, installation and servicing, etc., using design output data and information. For example, the finished device final-test methods and some installation and/or servicing test methods and data forms may be derived from the design verification protocol(s). When all of these design and documentation activities are completed, the DMR is complete. When the DMR is complete and initial production units, including
packaging, meets all specifications, the total finished design output exists.

To generate the design output per the QS regulation in 820.30(d), three activities are required. Each of these is listed and discussed below.

1. Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements.

2. Design output procedures shall contain or make reference to acceptance criteria and ensure that those design outputs that are essential for the proper functioning of the device are identified.

3. Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.

**Documenting Design Output (1)**

Documenting design output in terms that allow an adequate evaluation of conformance to design input requirements is a significant requirement and design activity. A common technique for achieving this conformance is listed below.

- Convert the general input requirements to specific design engineering specifications and give each item a line/paragraph number.

- Develop the design to meet all of the parameters and characteristics in the design engineering specification.

- Generate a verification requirement document(s) and test method(s) for the design and give each requirement/parameter/characteristic the same line/paragraph number that it has in the design engineering specification.

- Generate a verification data form that lists each requirement/parameter/characteristic and give each requirement/parameter/characteristic the same line/paragraph number that it has in the design engineering specification.

Each of these documents has a different drawing number but the line/paragraph numbers are the same. The first of these documents may be used as the beginning format for the next one. Therefore, it is almost impossible to leave out an element. Thereafter, when the verification is performed and documented, conformance or lack of conformance from input to output is known.

**Acceptance Criteria (2)**

The verification documents and data contain more information than is typically needed for production
evaluation and acceptance of components, in-process items and finished devices. Therefore, it is easy to copy and modify verification documents to meet the quality system requirement that: design output procedures shall contain or make reference to acceptance criteria and ensure that those design outputs that are essential for the proper functioning of the device are identified. In fact, this technique of deriving test procedures from the verification protocols also yields the test method(s) and data form(s) needed to meet the DMR requirements for QA procedures and acceptance criteria in 820.181(c).

**Design Output Approval (3)**

The third and final output requirement is that: design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented. This means that:

- Manufacturers may choose to have a group review certain documents and have individuals review other documents.

- Output documents that are directly part of the DMR are reviewed, dated and signed by the author which is current practice; and reviewed, dated and approved by individual(s) designated by the manufacturer. As appropriate, these reviews should cover technical issues as well as adequacy for use in production, purchasing, servicing, etc. DMR documents that are generated and approved under 820.30 automatically meet the approval requirements of 820.40, *Document Controls* and do not have to be re-approved under 820.40.

- Design output reports, data and any other document that will be used to create documents in the DMR are reviewed, dated and signed by the author which is current practice; and reviewed, dated and approved by individual(s) designated by the manufacturer.

Design output also includes the physical design which, of course, is not intended to be signed, and dated. The approval for the physical design is the validation that is done on initial production units.

**DESIGN VERIFICATION AND VALIDATION**

Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification [820.30(f)] shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

Validation [820.30(g)] means confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled.

Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.
Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.

Design verification is always done versus specifications. Therefore, to control the specifications and increase the probability of achieving desired safety and performance characteristics, device, software, labeling, packaging and any other specifications should be complete and thoroughly reviewed before development commences. As the hardware and software designs evolve, they should be evaluated versus their current specifications.

Verification and validation should be done with test equipment calibrated and controlled according to quality system requirements. Otherwise, there is limited confidence in the data.

Verification and validation should also be done according to a written protocol(s). The protocol(s) should include defined conditions for the testing. The protocol(s) should be approved before being used. Test protocol(s) are not perfect for a design, particularly a new design. Therefore, the designers and other verification personnel carefully annotate any ongoing changes to a protocol. Likewise, the verification personnel should record technical comments about any deviations or other events that occurred during the testing. The slightest problem should not be ignored. During design reviews, the comments, notes and deviations may be as important as test data from the formal protocol(s).

**Design Evaluation versus Specifications**

The original design of devices and any subsequent changes should be verified by appropriate and formal laboratory, animal, and in vitro testing. Risk analysis should be conducted to identify possible hazards associated with the design. Failure Mode Effects Analysis and Fault Tree Analysis are examples of risk analysis techniques.

Appropriate laboratory and animal testing followed by analysis of the results should be carefully performed before clinical testing or commercial distribution of the devices. The manufacturer should be assured that the design is safe and effective to the extent that can be determined by various scientific tests and analysis before clinical testing on humans or use by humans. For example, the electrical, thermal,
mechanical, chemical, radiation, etc., safety of devices usually can be determined by laboratory tests.

Clinical testing is not needed for many substantially equivalent devices (See 21 CFR Part 807 Subpart E - Premarket Notification Procedure). Where it is needed, such as for complex substantially equivalent devices or new devices, clinical testing on humans should meet the applicable requirements in the Investigational Device Exemption (IDE) regulations (21 CFR Parts 812 and 813).

The general IDE regulation (21 CFR Part 812) exempts a manufacturer during the "premarketing phase" from the following provisions of the FD&C Act:

- Misbranding,
- Registration of the Establishment,
- Premarket Notification [510(k)],
- FDA Performance Standards,
- Premarket Approval,
- **Production sections ONLY** of the Good Manufacturing Practices,
- Color Additives,
- Banned Devices, and
- Restricted Devices.

Don't be misled by this list of exemptions -- being exempted from these provisions does not mean that a manufacturer may develop a new device under uncontrolled conditions and then test it on humans. Devices being clinically tested are not exempt from section 501(c) of the FD&C Act, which states that a device is adulterated if it does not meet a manufacturer's quality claims. Devices being manufactured for use in clinical studies under an IDE are exempt ONLY from the production section of the QS regulation. They are not exempt from design controls listed in 820.30. In addition, the IDE regulation has labeling requirements in 812.5 and quality assurance requirements in 812.20(b)(3) that shall be met. Further, manufacturers should remember that human subjects are also protected through the courts via product liability laws and actions. In summation, protection of manufacturer interests, human test subjects, practitioners, and patients requires that all medical devices be developed, evaluated, and manufactured under a total quality system.

Laboratory testing to force a failure takes considerable time and the "culprit" may not fail during the testing. Another evaluation technique is Failure Mode and Effects Analysis (FMEA) in which failures are assumed to occur. FMEA is useful for evaluating reliability, safety, and general quality where, for example, the evaluator assumes that:

- each component fails,
- each subsystem or subassembly fails,
- the operator makes errors, and
- the power source is interrupted and immediately restarted.

The probability of each failure actually occurring and, if it does, the resulting effect are analyzed. Then,
where needed and feasible, hazards and faulty performance are designed out of the device or reduced; or compensated or prevented/reduced by interlocks, warning signs, explicit instructions, alarms, etc. Risks, of course, cannot always be removed from medical devices, but they should be known and controlled to the extent feasible with existing technology.

Failure Mode and Effects Analysis (FMEA) is a very powerful and cost-effective technique. Note that it takes very little time to assume that a component or subsystem is going to fail versus the time required to test to failure. The idea is not to promote one method above the other because a reasonable amount of both actual testing and failure mode and effects analysis should be done before a device is clinically tested and/or placed into production.

Besides using FMEA there are also other human factor and validation process techniques that can be used in developing an overall risk analysis. These techniques include: timelines, workload analysis, failure analysis, alternative calculations, testing including animal testing, auditing the design output, design reviews, demonstrations, and comparing a new design to a proven design etc. The users should be considered components when developing a fault tree and failure mode effects analysis.

All evaluation results should be reviewed by product development personnel who compare the tests and FMEA results with specifications, including safety and performance standards, to make certain that the desired level of intrinsic quality has been designed into the device. Also, the appropriate design of manufacturing processes, including validation where appropriate, is needed to assure that production can achieve the level of quality designed into the device.

Software Validation

Software is evaluated and reviewed versus the software specifications during the ongoing development of the device design. When a "final" prototype(s) is available, the software and hardware are validated to make certain manufacturer specifications for the device and process are met. Some aspects of hardware evaluation were discussed above. Aspects specific to software are covered below.

Before testing the software in actual use, the detailed code should be visually reviewed versus flow charts and specifications. All cases, especially decision points and error/limit handling, should be reviewed and the results documented.

In all cases, algorithms should be checked for accuracy. Recalls have occurred because algorithms were incorrectly copied from a source and, in other cases, because the source algorithm was incorrect. During the development phase, complex algorithms may need to be checked by using a test subroutine program written in a high-order language, if the operational program is written in a low-level language.

The validation program is planned and executed such that all relevant elements of the software and hardware are exercised and evaluated. The testing of software usually involves the use of an emulator and should include testing of the software in the finished device.
The testing includes normal operation of the complete device; and this phase of the validation program may be completed first to make certain that the device meets the fundamental performance, safety and labeling specifications. Concurrently or afterward, the combined system of hardware and software should be challenged with abnormal inputs and conditions. As appropriate, these inputs and conditions include such items as:

- operator errors;
- induced failure of sensors and cables or other interconnects;
- induced failure of output equipment;
- exposure to static electricity;
- power loss and restart;
- simultaneous inputs or interrupts; and,
- as appropriate, deliberate application of none, low, high, positive, negative, and extremely high input values.

The results of the software and combined device system validation are included in the design reviews.

**Labeling Verification**

During verification, the complete device is exercised such that all labeling, displays, and outputs are generated, reviewed, and the results documented. During the verification, all displayed prompts and instructions are checked versus the manufacturer's and FDA's labeling requirements and versus the operator manual.

Printed labeling and screen displays should be checked to see if they are directed to the user and not to the system designers, which is a common fault found in labeling. Displayed text should be short and to the point. Because displays are brief, keywords should be carefully selected to match system characteristics, yet transfer the maximum information to the user. The text of references to controls or other parts of the system should match the labeling on the device. Data, identifications, or other key information displayed should be current, complete, unambiguous, and accurate.

During verification, all prompts and instructions should be followed exactly by the device test or other operators and such action should result in correct operation of the device. Prompts and instructions should appropriately match the instructions in the operator's manual. The evaluation should include verification that any screen or other displays meet the requirements of, and have been approved per, the manufacturer's policy/procedure for design of labeling.

Patient and procedure data on printouts should be correct; therefore, printouts should undergo a verification similar to that performed for the screen or other displays. In addition, the printouts should be evaluated with respect to their "cold" information transfer characteristics. Will the printouts be quickly and clearly understood a few weeks later when the reader is not reading the displays, operating the device, or looking at the patient? All printouts should also meet the manufacturer's design control policy/procedure requirements for labeling. Likewise, patient data or other key information transmitted to a...
remote location should be correct; therefore, it should be checked for accuracy, completeness, and identification. Annotated copies of verified labeling, printouts, etc. and associated notes and any checklists should be placed in the design history file.

The overall device specifications usually have requirements that cover user/operator error prevention and control. Along with operator training, such errors are controlled by:

- adequate instruction manuals,
- adequate device labels,
- display of adequate prompts and correct instructions,
- status (history) reports,
- exclusion of certain erroneous inputs or actions, and
- adequate human factors design.

Also, for some devices, it may be important to control the order in which data can be entered by the operator. In emergency situations or because of distractions, it may be important to present the operator with a brief history or status report of recent actions. During the verification, the listed items should be evaluated versus the specifications, and checked for completeness and appropriateness. A checklist or matrix may be used to aid in the review of labeling.

**DESIGN TRANSFER**

The design controls require that each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications.

It is common practice for sections of a design to be transferred before the entire design is completed. The QS regulation does not prevent such split or multiple transfers. Transfer is to be performed only for completed elements of the design -- multiple transfers may not be used to bypass any design, labeling or other GMP requirements.

A significant part of the transfer requirement is met when the design output is being created. That is, some of the design output documents are part of the DMR and are used directly for production. The remaining DMR documents are based on design output information. A procedure is needed to cover the generation of the remaining device master record documents based on information in the design output documents.

Design transfer should assure that the section of the design being transferred:

- meets input requirements;
- contains acceptance criteria, where needed;
- contains design parameters which have been appropriately verified;
- is complete and approved for use;
is fully documented in the DMR or contains sufficient design output information to support the
generation of remaining DMR documents; and
is placed under change control if not already done.

Design transfer may include training of production, installation and service employees and such training
should be covered by or referenced by the transfer procedure.

DESIGN CHANGES

Changes to a design element are controlled per 820.30(i) Design Changes which states that: each
manufacturer shall establish and maintain procedures for the identification, documentation, validation or
where appropriate verification, review, and approval of design changes before their implementation.

The original design activities and subsequent change control activities for the design are both done under
the full set of the quality system design controls. A manufacturer may not use a design change control
procedure to bypass part of the design controls. Thus, it is difficult to describe change control before
design transfer because both activities are done under design controls.

Most of the details of the change control system are left to the manufacturer to develop, document and
implement. As the design activity progresses toward the final stage, it is expected that the degree of
change control will increase.

Those elements of the design that have been verified and accepted obviously should be under change
control. A design that has been submitted to FDA for marketing clearance should be under change
control. A design undergoing clinical trials should be under change control or the clinical data may not be
accepted by FDA. A design that is released for production should be under design and general change
control.

After design activities are begun and the physical design evolves into an accepted entity, subsequent
changes to the device specification(s) are proposed, evaluated, reviewed, approved, and documented per
all of 820.30. The revised specification(s) becomes the current design goal in accordance with the
manufacturer procedures for: design control, design change control, and document control.

A design change control procedure should at least cover:
under what conditions change control is required;
documenting the reason for the change;
any differences in the change control process when outside parties are involved;
analysis of the design to identify other elements that are impacted by the change; and
for significant changes which includes any change requiring verification and/or validation, placing
the reason for the change in the design history file along with the required design verification,
validation and review documentation.

DESIGN HISTORY FILE
Design history file (DHF) means a compilation of records which describes the design history of a finished device [820.3(e)].

The DHF covers the design activities used to develop the device, accessories, major components, labeling, packaging and production processes.

The design controls in 820.30(j) require that each manufacturer shall establish and maintain a DHF for each type of device. Each type of device means a device or family of devices that are manufactured according to one DMR. That is, if the variations in the family of devices are simple enough that they can be handled by minor variations on the drawings, then only one DMR exists. It is common practice to identify device variations on drawings by dash numbers. For this case, only one DHF could exist because only one set of related design documentation exists. Documents are never created just to go into the DHF.

The QS regulation also requires that the DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part. As noted, this requirement cannot be met unless the manufacturer develops and maintains plans that meet the design control requirements. The plans and subsequent updates should be part of the DHF. In addition, the QS regulation specifically requires that:

- the results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the DHF.

- design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

Typical documents that may be in, or referenced in, a DHF are listed below:

- design plans;
- design review meeting information;
- sketches;
- drawings;
- procedures;
- photos;
- engineering notebooks;
- component qualification information;
- biocompatibility (verification) protocols and data;
- design review notes;
- verification protocols and data for evaluating prototypes;
- validation protocols and data for initial finished devices;
- contractor / consultants information;
- parts of design output/DMR documents that show plans were followed; and
● parts of design output/DMR documents that show specifications were met.

The DHF contains documents such as the design plans and input requirements, preliminary input specs, validation data and preliminary versions of key DMR documents. These are needed to show that plans were created, followed and specifications were met.

The DHF is not required to contain all design documents or to contain the DMR, however, it will contain historical versions of key DMR documents that show how the design evolved.

Does the DHF have value for the manufacturer? Yes, when problems occur during re-design and for new designs, the DHF has the "institutional" memory of previous design activities. The DHF also contains valuable verification and validation protocols that are not in DMR. This information may be very valuable in helping to solve a problem; pointing to the correct direction to solve a problem; or, most important, preventing the manufacturer from repeating an already tried and found-to-be-useless design.

EXHIBITS

Design Input Requirements Procedure

A sample Design Input Requirements procedure is presented which covers basic activities for obtaining data on requirements that is needed for employees to develop device specifications. This procedure uses the multiple specification approach; however, a single combined specification would use a very similar procedure. This procedure should be modified to meet specific needs before being adopted by a manufacturer.

COMPANY LOGO

Title: Design Input Requirements Procedure SOP #: ____________ Page: _1_of_2_____

Prepared by: ____________________________ App: ____________ Date: ____________

Prep. Date: ____________________________ Rev: ____________ Date: ____________

ECN History: ____________________________________________________________________

POLICY - Design specifications covering all design requirements shall be established for all proposed devices before any significant physical design activities are started.
**SCOPE** - This policy applies to all devices and accessories developed by the manufacturer or developed by a contractor for us. For purchase of completed designs, refer to SOP ####. The device specification(s) must exist or be generated regardless of the source of the design.

**CONFIDENTIALITY** - Device development plans and activities are always confidential. Market research reports and documents such as specifications with parameter data shall be marked confidential.

Design control procedures, standard SOPs, blank forms, and required design review and design verification/validation records may be shown to, and may be copied by, FDA investigators as required by the QS regulation. Design parameters are not covered by the QS regulation. Therefore, confidential specification characteristics and parameters in the copies of these documents shall be blacked out unless the document is being collected during an inspection related to a marketing submission.

**RESPONSIBILITY**

Marketing and Engineering have the primary responsibility for determining safety and performance requirements and developing input specifications; however, all departments are expected to support the development of input requirements and subsequent specifications.

**MARKETING** - Marketing shall plan and conduct all customer contacts to obtain information on customer desires, needs, expected pricing, opinions about existing devices, etc.

To the maximum extent feasible, market research shall be conducted in a manner to reduce leaking of manufacturer confidential information and plans.

Design review meetings shall normally precede and follow all significant outside market research activities. Initial market research activities shall be previewed with top management.

Market research results are to be documented and marked confidential.

**PRODUCTION** - Production has primary responsibility for assuring producibility and establishing manufacturing requirements. Some of these requirements may be general during the early design stages.

**ENGINEERING** - Engineering is expected to supply design input information on most requirements. Such inputs may parallel data obtained by market research.

Engineering has primary responsibility for specifying what technology to use.

Engineering shall analyze input data on requirements and reduce it to preliminary specifications.

Engineering has primary responsibility for addressing incomplete, ambiguous, or conflicting requirements and shall see that such issues are appropriately discussed at design reviews.
RA & QA - RA and QA managers or their designees shall attend all design input or specification review meetings to provide input on, and to assure that, regulatory, manufacturer, quality, safety, performance, etc., procedures are followed and that requirements are met.

SPECIFICATIONS

STRUCTURE - Multiple specifications shall be used except for very simple devices. A separate specification shall be developed for accessories, labeling, packaging, etc. An overall device specification shall be developed and shall include an index that points to supporting specifications. The specifications, among other factors, shall address:

1. Performance and Efficacy;
2. Human Factors;
3. Chemical Safety;
4. Electrical Safety;
5. Mechanical Safety;
6. Radiation Safety;
7. Thermal Safety;
8. Biocompatibility;
9. Device Compatibility;
10. System Compatibility;
11. Environmental Compatibility;
12. Packaging (in a separate specification document);
13. Any FDA design requirements in the Part 801 and Part 1000-1050 regulations; and
14. Labeling in a separate document and, as appropriate, in the device primary specification.

CHECKLISTS - Checklists of requirements germane to our product line may be used to develop and support specifications. If used, such checklists become part of this procedure and part of the design documentation.

DESIGN REVIEW - Each specification shall undergo design review before it is approved for physical design activities or is used as a background document to support further market research. Such reviews shall be documented.

APPROVAL - The Marketing manager and Engineering manager shall approve all input specifications after these have been subjected to design review.

DOCUMENTATION - The approved specifications shall be given document numbers and become part
of the device master record for the new device.

**CHANGE CONTROL** - The Engineering manager shall decide when design activities have progressed to the stage that the various specifications shall be subject to our Design Change Control Procedure. However, for our organization, design change control can start NO later than the FIRST of the following events:

- clearance of a 510(k), or
- start of a clinical investigation.

Updated 1/1/1997
4. Process Validation

INTRODUCTION

The Quality System (QS) regulation defines process validation as establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications [820.3(z)(1)]. The requirement for process validation appears in section 820.75 of the Quality System (QS) regulation. The goal of a quality system is to consistently produce products that are fit for their intended use. Process validation is a key element in assuring that these principles and goals are met.

The process validation requirements stated in the QS regulation and the guidance offered here have general applicability to manufacturing processes for medical devices. Many technologies are used in the production of medical devices. The details of process validation will vary according to the nature of the...
medical device (e.g., sterile or non-sterile) and the nature and complexity of the process being validated.

Processes are developed according to the design controls in 820.30 and validated according to 820.75. The process specifications, hereafter called parameters, are derived from the specifications for the device, component or other entity to be produced by the process. The parameters are documented in the device master record per 820.30, 820.40 and 820.181. The process is developed such that the required parameters are achieved. To ensure that the output of the process will consistently meet the required parameters during routine production, the process is validated.

The basic principles for validation may be stated as follows:

- Establish that the process equipment has the capability of operating within required parameters;
- Demonstrate that controlling, monitoring, and/or measuring equipment and instrumentation are capable of operating within the parameters prescribed for the process equipment;
- Perform replicate cycles (runs) representing the required operational range of the equipment to demonstrate that the processes have been operated within the prescribed parameters for the process and that the output or product consistently meets predetermined specifications for quality and function; and
- Monitor the validated process during routine operation. As needed, requalify and recertify the equipment.

TERMS AND DEFINITIONS

Terms other than those used herein may be found in the literature.

Validation: confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled.

Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

Installation qualification: establishing documented evidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.

Process performance qualification: establishing documented evidence that the process is effective and reproducible.

Product performance qualification: establishing documented evidence through appropriate testing that
the finished product produced by a specified process(es) meets all release requirements for functionality and safety.

**Prospective validation:** validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

**Retrospective validation:** validation of a process for a product already in distribution based upon accumulated production, testing and control data.

**Validation protocol:** a written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

**WHY VALIDATE PROCESSES**

There are many reasons, in addition to the regulatory requirements, for validating processes. A manufacturer can assure through careful design of the device and packaging, careful design and validation of processes, and process controls, that there is a high probability that all manufactured units will meet specifications and have uniform quality. The dependence on intensive in-process and finished device testing can be reduced. However, in-process and finished product testing still play an important role in assuring that products meet specifications. A properly validated and controlled process will yield little scrap or rework, resulting in increased output. Consistent conformance to specifications is likely to result in fewer complaints and recalls. Also, when needed, the validation files contain data to support improvements in the process or the development of the next generation of the process.

**WHAT PROCESSES SHOULD BE VALIDATED**

Where process results cannot be fully verified during routine production by inspection and test, the process must be validated according to established procedures [820.75(a)]. When any of the conditions listed below exist, process validation is the only practical means for assuring that processes will consistently produce devices that meet their predetermined specifications:

- Routine end-product tests have insufficient sensitivity to verify the desired safety and efficacy of the finished devices;

- Clinical or destructive testing would be required to show that the manufacturing process has produced the desired result or product.¹ [see FOOTNOTES at end of this chapter]

- Routine end-product tests do not reveal all variations in safety and efficacy that may occur in the finished devices.² [RETURN from footnotes]
- The process capability is unknown, or it is suspected that the process is barely capable of meeting the device specifications.

**TYPES OF PROCESS VALIDATION**

Process validation may be conducted at different points during the life cycle of a product. The types of process validation are defined in terms of when they occur in relation to product design, transfer to production and release of the product for distribution.

**Prospective Validation**

Prospective validation is conducted before a new product is released for distribution or, where the revisions may affect the product's characteristics, before a product made under a revised manufacturing process is released for distribution.

Concurrent validation is a subset of prospective validation and is conducted with the intention of ultimately distributing product manufactured during the validation study. Concurrent validation is feasible when nondestructive testing is adequate to verify that products meet predetermined specifications and quality attributes. If concurrent validation is being conducted as the initial validation of a new process or a process which has been modified, product should be withheld from distribution until all data and results of the validation study have been reviewed, and it has been determined that the process has been adequately validated.

Concurrent validation may be conducted on a previously validated process to confirm that the process is validated. If there have been no changes to the process and no indications that the process is not operating in a state of control, product could be released for distribution before revalidation of the process is completed. There is some risk to early release of product in that subsequent analysis of data may show that the process is not validated.

**Retrospective Validation**

Retrospective validation is the validation of a process based on accumulated historical production, testing, control, and other information for a product already in production and distribution. This type of validation makes use of historical data and information which may be found in batch records, production log books, lot records, control charts, test and inspection results, customer complaints or lack of complaints, field failure reports, service reports, and audit reports. Historical data must contain enough information to provide an in-depth picture of how the process has been operating and whether the product has consistently met its specifications. Retrospective validation may not be feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis.

Incomplete information mitigates against conducting a successful retrospective validation. Some
examples of incomplete information are:

- Customer complaints which have not been fully investigated to determine the cause of the problem, including the identification of complaints that are due to process failures;
- Complaints were investigated but corrective action was not taken;
- Scrap and rework decisions that are not recorded, investigated and/or explained;
- Excessive rework;
- Records that do not show the degree of process variability and/or whether process variability is within the range of variation that is normal for that process, for example, recording test results as "pass" or "fail" instead of recording actual readings or measurements results in the loss of important data on process variability; and
- Gaps in batch records for which there are no explanations. (Retrospective validation cannot be initiated until the gaps in records can be filled or explained.)

If historical data is determined to be adequate and representative, an analysis can be conducted to determine whether the process has been operating in a state of control and has consistently produced product which meets its predetermined specifications and quality attributes. The analysis must be documented.

After a validated process has been operating for some time, retrospective validation can be successfully used to confirm continued validation of that process if no significant changes have been made to the process, components, or raw materials.

Statistical process control is a valuable tool for generating the type of data needed for retrospective analysis to revalidate a process and show that it continues to operate in a state of control.

**PROCESS VALIDATION STUDIES**

**Planning the Process Validation Study**

Careful planning of a validation study is essential to ensure that the process is adequately validated. The plan should include design reviews. The plan for the validation study is documented in the validation protocol. A copy of the protocol and validation results are placed in the Design History File (DHF) [820.30 (j)] or quality system record file (820.186). The operational, monitoring, and other production-related procedures are part of the device master record (DMR) (820.181). Planning for the validation should include the following elements as well as any other relevant issues that must be addressed to conduct the validation study:
- identification of the process to be validated;

- identification of device(s) to be manufactured using this process;

- criteria for a successful study;

- length and duration of the study;

- assumptions (shifts, operators, equipment, components);

- identification of equipment to be used in the process [820.75(b)(2)];

- identification of utilities for the process equipment and quality of the utilities;

- identification of operators and required operator qualifications [820.75(b)(2)];

- complete description of the process {may reference the DMR [820.181(b)]};

- relevant specifications including those for the product, components, manufacturing materials, the environment, etc. {may reference the DMR and quality system files {820.181(a) and (b); 820.186};

- any special controls or conditions to be placed on preceding processes during the validation;

- process parameters to be controlled and monitored, and methods for controlling and monitoring [820.70(a); 820.75(b)(2)];

- product characteristics to be monitored and method for monitoring [820.70(a)(2); 820.75(b)(2); 820.80(c)];

- any subjective criteria used to evaluate the product;

- definition of what constitutes nonconformance for both measurable and subjective criteria;

- statistical methods for data collection and analysis (820.250);

- consideration of maintenance and repairs [820.72(a)];

- conditions that may indicate that the process should be revalidated [820.75(c)];
The validation plan should also cover the installation and operation qualification of any equipment used in the process, process performance qualification, and product performance qualification.

**Installation and Operation Qualification**

After process equipment is designed or selected, it should be installed, reviewed, calibrated, challenged, and evaluated to ensure that it is capable of operating within established limits and tolerances as well as throughout all anticipated operating ranges. Installation and operation qualification studies establish confidence that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [820.70(g)].

The installation and operation qualification phases of process validation include:

- examining equipment design and supplied documentation;
- determining installation requirements;
- establishing any needed environmental controls and procedures;
- assuring that the work area has sufficient space to perform the processing and associated activities;
- installing the equipment;
- verifying correct installation;
- establishing manufacturing procedures for the monitoring, operation, and control of the equipment including the minimum number of operators;
- determining calibration, cleaning, maintenance, adjustment, and expected repair requirements;
- identifying important elements of the equipment that could affect the output or finished device;
- verifying that the system or subsystem performs as intended throughout all anticipated operating ranges; and
documenting the above information.

Equipment fabricators may perform qualification runs at their facilities and analyze the results to determine that the process equipment is ready for delivery to the medical device manufacturer. Device manufacturers should obtain copies of the suppliers' qualifications studies to use as guides, to obtain basic data, and to supplement their own qualification studies. However, it is usually insufficient to rely solely upon the representations and studies of the equipment supplier. The device manufacturer is ultimately responsible for evaluating, challenging, and testing the equipment and deciding whether the equipment is suitable for use in the manufacture of a specific device(s). The evaluations may result in changes to the equipment or process. Such changes must meet QS requirements in 820.30, Design Control; 820.40, Document Controls; 820.50, Purchasing Controls; 820.70, Process Controls; 820.72, Inspection, Measuring, and Test Equipment; 820.75, Process Validation; 820.181, Device Master Record.

Installation and operation qualifications should include establishing pertinent methods, procedures, and schedules for calibration, cleaning, and maintenance, and establishing a repair parts list for each piece of equipment. Planning for eventual maintenance and repairs can reduce or prevent confusion during emergency repairs which could lead to improper repairs such as the use of the wrong replacement part. Post-repair cleaning, calibration, and re-start requirements should be established if necessary to prevent inadvertent manufacture of nonconforming devices. The objective is to assure that all repairs can be performed in a way that will not affect the characteristics of material processed or devices manufactured after repairs.

Process and monitoring equipment (instruments) should be calibrated at the beginning of the validation study, and the calibration should be checked at the end of the study to establish confidence in the validation of the process. Equipment found out of calibration at the end of a process validation study may indicate that the process has not been operating in a state of control and cannot be considered validated. More frequent calibration or more robust equipment may be necessary, or you may wish to use stand-alone instruments in parallel with the built-in process monitoring equipment.

It is important to document installation and operation qualification studies. Such documentation can substitute for part of the requalification of equipment in future process validation studies. When equipment is moved to a new location, installation and operation should be requalified. By comparing data from the original installation and operation qualification and the requalification, the manufacturer can determine whether there have been any changes in equipment performance as a result of the move. Changes in equipment performance should be evaluated to determine whether it is necessary to revalidate the process.

**Process Performance Qualification**

The purpose of process performance qualification is to rigorously test the process to determine whether it is capable of consistently producing an output or in-process or finished devices which meet
specifications. In entering the process performance qualification phase of validation, it is understood that the:

- device, packaging, and process specifications have been established, documented, and essentially proven acceptable through engineering, laboratory or other verification methods [820.30; 820.70(a)]; and

- process and ancillary equipment and the environment have been judged acceptable on the basis of installation and operation qualification studies [820.70(g)].

Challenges to the process should simulate conditions that will be encountered during actual production. Challenges should include the range of conditions allowed in written standard operating procedures and should be repeated enough times to assure that the results are meaningful and consistent. Challenges may need to include forcing the preceding process to operate at its allowed upper and lower limits.

Process and product data should be analyzed to determine what the normal range of variation is for the process output. Knowing what is the normal variation of the output is crucial in determining whether a process is operating in a state of control and is capable of consistently producing the specified output.

Process and product data should also be analyzed to identify any variation due to controllable causes. Depending on the nature of the process and its sensitivity, controllable causes of variation may include:

- temperature,
- humidity,
- variations in electrical supply,
- vibration,
- environmental contaminants,
- purity of process water,
- light, and
- inadequate employee training.

Appropriate measures should be taken to eliminate controllable causes of variation. For example, extreme variations in temperature can be eliminated by installing heating and air conditioning. Employee training can be improved and conducted more frequently, and employees can be monitored more closely to assure that they are properly performing the process. Eliminating controllable causes of variation will reduce variation in the process output and result in a higher degree of assurance that the output will consistently meet specifications.

After routine production begins, data derived from monitoring the process and output product can be analyzed for variation and compared to the normal range of variation. Such analyses can detect when the process output is shifting so that corrections can be made before, or soon after, nonconforming product is produced.
**Product Performance Qualification**

The purpose of *product* performance qualification is to demonstrate that the process has not adversely affected the finished product and that the product meets its predetermined specifications and quality attributes. Product performance qualification and design validation of initial finished devices are closely related. According to the design control requirements, design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents [820.30(g)]. Products used for design validation should be manufactured using the same production equipment, methods and procedures that will be used in routine production. Otherwise, the product used for design validation may not be representative of production units and cannot be used as evidence that the manufacturing process will produce a product that meets pre-determined specifications and quality attributes.

Design validation can be conducted using finished products made during process validation studies and will satisfy the need for product performance qualification. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing production units under actual or simulated use conditions [820.30(g)]. Original designs and design changes are subject to design control requirements [820.30(i)]. The results of design validation are subject to review under the design control review requirements [820.30(e)].

**DOCUMENTATION**

The requirements for process validation are described in section 820.75 and include documentation requirements for the process validation study phase as well as for routine production using a validated process. Records of validation activities and results must be maintained [820.75(a)]. Validation protocols and results may be filed in the DHF [820.30(j)] or in the QS files (820.186). Records must include the date and signature of the individual(s) approving the validation and, where appropriate, the major equipment validated [820.75(a)]. Procedures for monitoring and control of process parameters must be established and maintained for validated processes [820.75(b)]. Procedures for the operation, monitoring and control of processes are part of the DMR (820.181).

When a validated process is used for manufacturing finished devices, the process must be performed by a qualified individual [820.75(b)(1)]. Records must be maintained of the monitoring and control methods and data; where appropriate, the individual(s) performing the process; the date performed; and major equipment used. The records should be maintained in the DHR (820.184).

**REVALIDATION**

As long as the process operates in a state of control and no changes have been made to the process or output product, the process does not have to be revalidated. Whether the process is operating in a state of control is determined by analyzing day-to-day process control data and any finished device testing data.
for conformance with specifications and for variability.

When changes or process deviations occur, the process must be reviewed and evaluated, and revalidation must be performed where appropriate [820.75(c)]. Review, evaluation, and revalidation activities must be documented.

Processes may be routinely validated on a periodic basis; however, periodic validation may not be adequate. More important is appropriate monitoring so that if problems develop or changes are made, the need for immediate revalidation is considered.

REFERENCES

1. Guideline on General Principles of Process Validation, May 1987, FDA, CDRH/CDER


FOOTNOTES

1. For example, USP 23 states: "Absolute sterility cannot be practically demonstrated without complete destruction of every finished article." [Added note: Also, a positive test result may be caused by operator error rather than non sterility.]

2. For example, visual inspections usually are not capable of detecting defects in structural welds. Such defects may be detectable only by using destructive testing, expensive test equipment, or very slow test methods. [RETURN to text above]

Updated 1/1/1997
5. Personnel and Training

INTRODUCTION

Establishing a quality system should be an integrated and universal effort. A total quality systems approach should be designed to satisfy the particular quality, safety, and performance needs of a specific manufacturer, product, and user-market. Employees play a vital role in achieving these objectives. Obviously, employees need to be aware of the details of the quality system and how to meet them. The Quality System (QS) regulation supports these goals by requiring that a manufacturer have sufficient qualified personnel and by requiring quality awareness training for personnel [820.25(a)]. Management with executive responsibility shall ensure their quality policy is understood, implemented, and maintained at all levels of the organization. This should be accomplished by supplying sufficient resources, training, responsibility, and authority to all managing personnel that will enable them to perform their tasks.

Personnel involved in design, manufacturing, quality assurance, auditing, complaint processing, servicing, etc., should be properly trained, both by education and experience. No matter how effective quality assurance and production systems are as concepts, people still play the major role in designing and producing a quality product. Lack of training -- as reflected in instances of negligence, poor operating techniques, or the inability of employees to discharge their functions properly -- can lead to defective products and, sometimes, to regulatory or liability problems.

Employee attitude is the most important personnel factor that can assure an effective quality system. By management setting an excellent example and through effective training, quality consciousness should be developed in every employee. Each person should be made aware of the importance of his or her individual contributions in the overall effort to achieve an acceptable level of quality.

The role of management in this vital awareness effort cannot be passive -- management should be diligent in looking for factors that indicate a need for employee training [820.25(b)]. A quality system should include an ongoing formal program for training all
personnel. All personnel should be made aware that product quality is not solely the responsibility of management or any other single group. Quality is the responsibility of every employee -- any employee can generate a quality problem through ignorance of their job requirements or negligence.

**FDA Observations**

It is not unusual for FDA investigators to conduct factory inspections and observe employees who are clearly unaware of situations that can result in poor device quality. These employees obviously have not been properly instructed on what activities or conditions will directly cause defective devices or that can lead to mixups, contamination, or other problems that can cause non-conforming devices. For example, an improperly maintained piece of manufacturing equipment may eventually have disastrous consequences on finished devices. Therefore, the employee charged with maintaining the equipment, as well as the operator of the equipment, should be made aware of conditions that reflect a need for maintenance.

FDA investigators have observed employees: smoking near or sweeping dust into open processing tanks where the smoke and dust would destroy the usefulness of the device; blowing smoke or sweeping dust onto devices to be sterilized; handling delicate devices while wearing rings or other jewelry; wearing gloves with holes or rubbing their nose and continuing to handle devices that need to comply with bioburden requirements; wearing cleanroom clothing into uncontrolled areas; and other poor practices such as leaving windows or doors open in controlled environmental areas.

FDA investigators were advised by management that it is the manufacturer's policy not to allow the above situations to occur. The implementation of this policy is questionable. Are these employees originally and then periodically reminded of the reason: for not smoking, eating, and wearing rings; and for personal cleanliness, and other employee requirements? People respond better when they know why they are allowed or not allowed to do certain activities - not just being told that it is company policy.

**GMP REQUIREMENTS**

The QS regulation requires in section 820.25 that each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed. [The requirement for sufficient trained personnel is also covered by resource requirements in 820.20(b)(2) as follows. Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities, including internal quality audits, to meet the requirements of this part.]

Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. [In addition to training, personnel also have to be notified if they are responsible for nonconforming product. The intent is to prevent or reduce nonconforming product. Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements [820.90(a)]. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented.]

Personnel who perform verification and validation shall be made aware of defects and errors that may be encountered as part of their job functions. There are also personnel requirements in 820.70(d) and 820.75(b)(1) as follows. Each manufacturer shall establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturers shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual.

Each manufacturer shall ensure that validated processes are performed by qualified individual(s) [870.75(b)(1)].

**Employee Selection**
As the first step in meeting GMP personnel requirements, manufacturers should select or hire appropriate employees for the tasks to be performed. The initial selection of employees for a specific job is made based on a combination of education, experience, personal habits, interests, etc. For example, education alone is not a good indicator of whether a recent graduate with a scientific degree can design a product.

New employees should be informed that they are working in a regulated industry and should be initially trained to perform their specific jobs and be made aware of any defects or problems that may occur from:

- improper performance of their assigned tasks;
- using incorrect tools or incorrect use of a tool;
- poor hygiene, poor health, or smoking or eating on the job;
- poor work habits or being in the wrong location; and
- other detrimental factors.

Production Personnel

Section 820.70(d) requires that personnel in contact with a device or its environment shall be clean, healthy, and suitably attired where lack of cleanliness, good health, or suitable attire could adversely affect the device. Personnel who, by medical examination or supervisory observation, appear to have a condition which could adversely affect the device should be excluded from affected operations until the adverse condition is corrected. Personnel should be instructed to report such conditions to their supervisor. Such actions by management could create problems unless employees are instructed about work practices and requirements when they are hired or initially assigned to the task in an environmentally controlled area.

If eating, drinking, or smoking could have an adverse affect on the devices' fitness for use, then employees should be informed that these activities are to be done only in designated areas.

Employees need to be informed why certain personnel and work practices are required. Basic instructions about invisible microorganisms and particulates will make the company requirements much more meaningful. People respond better when they know why they are allowed or not allowed to do certain activities rather than just being told it is company policy.

Some factors that should be considered when teaching employees about working in a controlled environment include:

- proper attire and dressing anteroom;
- controlled use of, and entry into, controlled areas;
- minimizing body movements;
- locating the body and hands with respect to product and airflow;
- prohibiting eating, drinking, smoking, or gum chewing;
- reducing of coughing, sneezing and other objectionable health related conditions;
- preventing use of lead pencils and certain cosmetics;
- bathing and hand washing requirements;
- preventing or controlling the cutting, tearing or storage of cardboard, paper, debris, etc.;
- eliminating electrostatic charges by selection of clothing, grounding, etc.;
- ensuring cleanliness of raw materials, components and tools; etc.
- using correct furniture and eliminating use of extra furniture;
- regulating the storage of tools, glassware and containers;
- cleaning the room and production equipment per written procedure; and
- cleaning of work surfaces and chairs.

Technical Personnel

The manufacturer should assure that they have sufficient properly trained personnel, or programs to train technical personnel, to design, validate, develop processes, and produce the new or modified device. Scientific and technical personnel usually need
training in:

- regulatory requirements;
- company documentation systems;
- verification and validation techniques;
- consensus standards;
- human factors;
- labeling;
- safety;
- reliability;
- producibility; and,
- other peripheral design topics.

New design personnel may be introduced to manufacturing methods and producibility issues by being assigned to various manufacturing areas before starting their design activities. The resulting knowledge and experience is as valuable as their technical education -- remember that the ultimate objective of a design and manufacturing operation is to produce a safe and effective device.

In another valuable training technique, manufacturing personnel are assigned to assist development personnel in verifying components, and assembling and verifying subassemblies and prototype devices.

These training techniques:

- improve communications and technology transfer between the various departments;
- help meet the interface requirements in 820.30(b), Design and Development Planning;
- help promote concurrent engineering;
- help research and development personnel understand that the goal is to produce a device -- not just design a device;
- achieve advance training for manufacturing personnel about a forthcoming design;
- reduce production problems by improving the producibility of the device based on the expertise and input of the manufacturing personnel into the design of the device; and
- reduce production problems based on the expertise and input of the device design personnel into the design of processes and production tools, jigs, molds, in-house standards, and test methods.

All of these are important and valuable side benefits to these simple cross-training techniques. Such training should be documented.

**Process Validation**

The above discussion for technical personnel also applies to technical employees that perform process validation. After the processes are validated, these technical personnel should use their expertise and experience to develop training methods or help train production employees on how to monitor, control, and operate validated processes. Section 820.75(b) requires a manufacturer to establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that specified requirements continue to be met. Further, 820.75(b)(1) requires that validated processes be performed by qualified individuals. Obviously, operators that are trained to operate each specific validated process are needed to meet these requirements.
During the development and validation of a process, planning for eventual maintenance can reduce or prevent confusion during emergency repairs. An emergency could lead to improper repairs, such as use of a wrong replacement part. Therefore, the installation qualification should include a review of pertinent training requirements, maintenance procedures, repair parts lists, and calibration of measuring equipment.

Quality Assurance Personnel

QA or product acceptance employees shall meet the GMP personnel requirements for manufacturing employees AND shall be made aware of defects and errors likely to be found in nonconforming components and devices. Usually, it is easier and more effective to teach all of the GMP personnel requirements to all appropriate employees.

Production or QA personnel performing quality assurance or acceptance functions should:

- Maintain requirements for health, cleanliness, and clothing standards which will prevent an adverse effect on product quality.

- Adequately train and/or supervise temporary personnel working in special environmental conditions.

The production department shall have sufficient personnel with the necessary education, background, training, and experience to assure that all production activities are correctly performed. Employees are selected and/or trained for their assigned tasks. These tasks may be janitorial, receiving, pulling parts, production, labeling, acceptance test and inspection, packaging, painting, welding, mixing, specific technical tests, etc.

To meet this requirement, each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities.

As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. Employees should be informed that they may need to be qualified or certified to perform certain tasks such as welding, operating a validated process or working in controlled areas. Likewise, employees need to be told that where necessary, they will be informed about improper performance of their assign tasks with the intent of improving their performance and reducing the likelihood of producing nonconforming product. Where necessary, employees should be certified to perform manufacturing or quality acceptance procedures where a high degree of specialized skill is required. Training shall be documented.

Complaint Handling

It is a good idea for most of the company personnel to receive basic training in complaint handling techniques. Appropriate employees such as receptionists, salespersons, representatives, secretaries, service personnel, and other employees who talk with users should receive training on their responsibilities in regard to complaint handling requirements in section 820.198. If these employees receive a device complaint, they need to know they have a responsibility to report it to the company person(s) assigned to handle complaints. Likewise, importers and distributors should be made aware of the complaint requirements, and they should be requested to forward complaints to the manufacturer.

Management

Proper job performance by employees as required by the QS regulation dictates that management have a good knowledge of the QS regulation and resulting quality system. Therefore, management should also have appropriate education, training, and experience. As part of their review of the quality system, management should make certain that adequate "how to do" documentation is available to employees. Proper job performance should be supported by correct and complete quality system and device master records. These records should be written in such a manner that the intended employees can understand and properly use them.

Management should show their commitment to training by providing a training room such as a cafeteria and training equipment
such as chalkboards, flip charts, video cameras, VCRs, television monitors, slide projectors, overhead projectors, screens, workbooks, etc.

**Training Methods**

Training for employees may be achieved by many methods such as:

- device regulatory and GMP seminars;
- individual consultations with managers, consultants, FDA personnel, etc.;
- on-the-job training with appropriate instructors;
- cross-training details between R&D and production;
- video tapes and movies;
- slide shows with an appropriate instructor;
- reading GMP/QA manuals and textbooks; and
- formal college QA courses.

To meet GMP requirements, all training should be documented as noted above.

**Training Indicators**

A proactive approach to training is required by 820.25(b) where each manufacturer is required to establish procedures for identifying training needs. Thus, management should diligently look for factors that indicate a need for additional training or retraining. Some of these training indicators are:

- verification failures due to basic problems,
- post-submission technical and labeling information required by ODE for 510(k) submissions,
- validation problems due to routine problems,
- excessive design transfer problems or delays,
- inadequate device master record,
- excessive device defects,
- excessive process equipment or line down-time,
- improper labeling or packaging,
- employee confusion,
- employees ignoring environmental control requirements,
- process or sterilization failures,
- incorrect ordering or shipment information,
- customer complaints, and
- excessive or basic items on a FDA list of observations.

This information is derived from management observations, analysis of device history records, analysis of complaint records, quality assurance audits, etc.

**Audits**

As management performs their daily activities they are aware of the obvious aspects of personnel workmanship and work practices. However, to make sure that all aspects, obvious, hidden, or subtle, of the required quality system exist and are operating correctly, the QS regulation in 820.20(b) requires planned and periodic audits of the quality system. This audit covers:

- noting personnel practices in areas being audited,
- looking for training indicators as listed above, and
- whether the company approach to training programs is proactive.
The audit also includes an inspection and review of training:

- programs and content,
- facilities,
- equipment, and
- records.

A report should be made of each quality audit, including any reaudits(s) of deficient matters such as incorrect performance of work, lack of training, failure to update training, the training program not being proactive for all of the personnel that receive complaints, part of the training equipment is not functioning, on-the-job training not adequately supervised or documented, etc. Audit reports that cover training activities and personnel practices should be reviewed by management responsible for these factors in their department. Corrective actions for deficient training and personnel practices shall be taken where necessary (820.22).

EXHIBITS

Reprinted on the following pages is an example of an employee general training procedure and an example of associated employee training record. These may be used to comply with the training requirements of the QS regulation.

The Buildings and Environment Chapter 6 has a procedure with many details about employee practices in clean rooms.

Employee Training Procedure

This procedure is an example of a general employee training procedure that may be used by manufacturers to assure that all employees receive basic training when they are hired and are qualified for the assigned tasks. The procedure is used with the following training form.

Employee Training Record

This employee training record is a basic form for noting training activities for each employee. A few training requirements are preprinted on the form because new hires should immediately receive this basic training. The training record is used with a general training procedure as described above.

*** SAMPLE PROCEDURE ***

COMPANY LOGO Page 1 of 2

Title Employee Training SOP Number ____________

Prepared by __________________________ Date Prepared __________

Approved by __________________________ Date Rev __________

ECN Notes ____________________________________________

Policy - Employees shall be trained as needed to perform their assigned tasks and shall be made aware that we produce medical devices in accordance with various regulations and standards.
**Scope** - This procedure applies to all employees.

**Hiring** - The education, background, training, and experience of prospective employees shall be considered with respect to the requirements of the job to be filled.

**Responsibility** - Managers are responsible for assuring that the employees assigned to them are trained or otherwise qualified for the assigned jobs. Before assigning an employee for the first time to a new job, managers shall check their training to verify that the employee has been trained or qualified for the new job.

The QA department is responsible for training facilities, equipment, and supplies.

**Training** - All inexperienced employees shall be trained to perform their assigned jobs. On-the-job training shall be monitored closely by a supervisor. All employees shall be made aware of design and/or production defects, visible and invisible, in the device, labeling, and packaging that may occur from the improper performance of their jobs and defects that they should look for and detect. Our cleanliness (environmental control) and safety procedures shall be explained to all employees.

**Quality Assurance Employees** - QA or product acceptance employees shall receive the training noted above and shall be made aware of errors and defects, visible and invisible, likely to be encountered as part of their quality assurance functions.

**Customer Complaints** - Receptionists, managers, representatives, salespersons, and other employees likely to receive complaints are trained in complaint handling procedures applicable to their functions.

**Change Control** - All employees are to be advised that they are to perform their jobs as instructed or as covered by standard operating procedures (SOP's). They are NOT allowed to change cleaning, compounding, processing, testing, packaging, labeling, or tasks covered by SOP's until the change is approved according to our change control SOP.

**Documentation** - All classroom and on-the-job training shall be documented by the supervisor and trainer of the employee on the form as shown on sheet 2. A separate form for each employee with a record of their training shall be filed and shall be updated at the end of each training session.

*** SAMPLE RECORD ***

<table>
<thead>
<tr>
<th>EMPLOYEE TRAINING RECORD</th>
<th>Page 2 of 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Employee Name</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hire Date</strong></td>
<td></td>
</tr>
<tr>
<td><strong>DATE</strong></td>
<td><strong>EMPLOYEE</strong></td>
</tr>
<tr>
<td></td>
<td><strong>SIGNATURE</strong></td>
</tr>
<tr>
<td><strong>PRESENT JOB</strong></td>
<td><strong>TYPE OF</strong></td>
</tr>
<tr>
<td></td>
<td><strong>TRAINING</strong></td>
</tr>
<tr>
<td></td>
<td><strong>SUPERVISOR /</strong></td>
</tr>
<tr>
<td></td>
<td><strong>TRAINER SIGN.</strong></td>
</tr>
<tr>
<td></td>
<td>safety</td>
</tr>
<tr>
<td></td>
<td>defect awareness</td>
</tr>
<tr>
<td></td>
<td>environment control</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
6. Buildings and Environment

INTRODUCTION

The buildings and environment in which components, devices, and records are received, processed, built, or stored, and the personnel that perform these operations should be controlled so that finished devices will consistently meet the specifications established by the manufacturer. The degree of control should allow for appropriate changes in such elements as temperature, humidity, bioburden, particles, personnel, components, devices, and records.

PERSONNEL TRAINING

Personnel play an important role in orderly operations and environmental control. They can reduce or increase contamination. Thus, personnel can positively or negatively impact most of the points made in this chapter. To reduce problems and increase the state-of-control, employees shall be appropriately trained regarding orderly operations and environmental control as required by 820.25 and as discussed in Chapter 5.

BUILDINGS

Facilities of medical device manufacturers and their contractors in which components, in-process devices, accessories, and finished devices are handled, processed, and stored shall have sufficient space and be designed to allow proper cleaning, maintenance, and other necessary operations in order to meet the requirements of 21 CFR 820.70 of the Quality System (QS) regulation. Buildings should be suitably designed so that there is adequate space for manufacturing, receiving, packaging/labeling, storage, etc., to: minimize contaminants; assure orderly handling procedures; and prevent mixups. As the company grows or the product line is changed, existing facilities may become inadequate. Thus, as part of the quality assurance program audit, existing buildings should be reviewed to determine if space and facilities are adequate in light of growth or changes in production.
Repackers, Remanufacturers, Contract Sterilizers, and Relabelers

The GMP requirements for buildings extend to manufacturers that repackage and/or relabel unpackaged bulk devices, contract sterilizers, and remanufacturers that change the original condition of devices. The number of operations needed to repackage or relabel a product may be less than for actual manufacturing of a product; nevertheless, there is a need to design and arrange facilities so that repackaging and/or relabeling operations, particularly for sterile devices, can be performed in a controlled manner. Because remanufacturing of devices is manufacturing, the GMP requirements for buildings and facilities extend to areas where modifications are performed. In some manufacturers these modifications are done in cluttered repair shops. Under these conditions, there is an increased probability for contamination or mixup, hence such manufacturers should take appropriate precautions as required by the QS regulation.

Contamination Control

Typical problems in manufacturing and storage facilities include environmental contamination and insufficient space for receiving and holding incoming products before testing and inspection [820.70(c) and 820.70(e) and 820.70(f)]. For each area in the building where products are processed, any elements such as particulates from cardboard dust, by-products from slitting or cutting operations, microorganisms, humidity, temperature, static electricity, etc., which a manufacturer has determined might cause contamination should be controlled. Buildings should be appropriately constructed to prevent, reduce, and control potential contaminants and support the environmental control program as discussed later. For example, the control of dust may require that driveways and parking lots be paved. Crowding causes mixups and can result in contamination or in the use of unapproved or rejected products. Designated areas should be assigned for various production activities such as receiving, inspection/testing, manufacturing, labeling, packaging, record keeping, etc. Traffic by personnel who do not work in or manage the designated areas should be held to a minimum.

Orderly Operations

In addition to having sufficient space, the facility shall be designed and arranged so that all operations can be performed in an orderly manner [820.70(f)]. This will facilitate the satisfactory performance of all operations. In manufacturing areas, it prevents confusion that can lead to unsatisfactory job performance and mixups. The goal is for a smooth flow of operations.

To preclude mixups, distinct operations or processes should be separated either physically, by walls or partitions, or spatially, by providing enough room between operations to indicate that separate activities are being performed. An appropriate degree of separation, or walls, curtains, etc., should exist so that no activity will spray, dust, or otherwise have an adverse effect on other adjacent activities. For example, there should be a handling and storage system to preclude the mixup of labeled "sterile" but not-yet-sterilized devices from the same type of devices that have been sterilized. Manufacturers that have more than one labeling operation should maintain adequate separation of these to prevent any mixups occurring between various products and their specified labeling. Labeling mixups are a major cause of product recalls and a number of these mixups can be traced to inadequate separation of operations during the labeling of devices.

ENVIRONMENTAL CONTROL

One of the variables that can significantly affect product quality and employee performance is the environment. A controlled environment is, to various degrees, an integral part of most production facilities. Some environmental factors to be considered are lighting, ventilation, temperature, humidity, pressure, particulates, and static electricity. Section 820.70(c), Environmental Control, of the QS regulation, is considered by FDA to be a "discretionary" requirement; that is, the degree of environmental control to be maintained should be consistent with the intended use of the device and details of how to achieve this control are left to the manufacturer to decide. "Discretionary quality system requirements" are those which may or may not apply to the manufacturer of a specific device. In these cases the manufacturer should decide whether implementing such requirements is necessary to assure the quality of the finished device. These requirements are modified in the QS regulation by phrases such as "where environmental conditions could reasonably be expected to have an adverse affect" and "adequately control."

General Controls

General air conditioning is normally not regarded as an environmental control; however, changes in temperature and lighting can have an adverse effect on employee performance and, in turn, on assuring that the device is properly assembled, inspected, and tested. Air conditioning can control humidity which, in turn, can affect the generation of static charges. Static charges can damage some electronic components and, in such situations, need to be controlled [820.70(c)]. Production workers are a major source of particulate contamination.
and standard operating procedures for personnel are often necessary in order that employees not adversely affect the environment.

**Analyze Operation**

If the environment in which devices are manufactured or held can have an adverse effect on the devices' fitness for use, that environment shall be controlled [820.70(c)]. For each operation, the manufacturer should analyze the manufacturing operations to identify controls needed for the finished device to meet the device specifications and be fit for the intended use; and to control costs. For example, in the manufacture of sterile devices such as implants, or diagnostic media that requires aseptic filling, the environment should be controlled to reduce viable microorganisms and particulate matter. The packaging for sterile devices should be stored in a clean, dry, insect-free area. Components that support bacterial growth should be stored in a controlled environment which, in some cases, will include refrigeration.

Because particles can bridge across sub-micron circuits and static electricity can rupture semiconductor junctions, microcircuits for use in devices should be manufactured in a stringent clean-room environment where particulates and humidity are controlled. When analyzing the production of a device to determine the degree of control needed, the manufacturer should identify exactly what needs to be controlled:

- the device itself;
- the area for one task; or
- the large production area.

For example, if the device can be cleaned after production, there usually is no need for extensive environmental control during production. If the cleaned devices are stored in clean containers or are immediately packaged, the environment usually should be controlled where the device is being packaged. If the work area needs to be controlled, how much should be controlled -- a work bench, room, or factory? For example, a HEPA filtered laminar-flow bench maintains a low-particulate environment that is large enough for many small tasks or operations. If a larger area is needed, then it may be possible to set a broad environmental specification for most of the room or area. A small laminar-flow unit and curtains can create a small, but very clean area. Considerations such as these can reduce environmental facility and equipment costs and reduce the activities required to maintain and monitor the controlled area and operations.

**Specifications**

When it is necessary to control the environment, specifications for parameters such as temperature, humidity, colony forming units (CFU's), and particulates per cubic foot, etc. should be established. No FDA guidances for these parameters presently exist for environmentally controlled areas such as clean rooms. "Federal Standard Airborne Particulate Cleanliness Classes In Clean room and Clean Zones" (FED-STD-209E) with its appendices is suggested as a resource for developing clean room standards such as particle counts per cubic foot. Federal Standard 209E defines various levels of environmental control such as Class 1000. A Class 1000 room contains no more than 1000 particles 0.5 micron diameter or larger per cubic foot of air. Information may also be obtained from manufacturers of clean room equipment. Aseptic manufacturing and filling are usually done in a Class 100 or better clean room or bench. The Class 100 status is maintained during routine operations. During idle periods the particle count will generally be much lower than 100. Some manufacturers use a Class 10,000 clean room for the assembly and packaging of devices that will be terminally sterilized and where a low particulate count on the devices is desired. The specifications for such a room could be:

| Particulates: Maximum of 10,000 of 0.5 micron diameter or larger per cubic foot |
| Humidity: 45 +/- 5 percent |
| Temperature: 72 +/- 2.5 degrees F |
| Air Velocity: 90 feet/minute +/- 2 percent |
| Air Pressure: 0.05 inches water between the clean room and other areas |

For assembly of many types of convenience kits and assembly of medical devices that need to be free of visible particles, many manufacturers use an "industrially clean area or controlled environment area." Such rooms are air conditioned and use furnace filters and, in some cases, pre-filters of much finer porosity than furnace filters are also used. The temperature is controlled by a standard room thermostat. Humidity variations are limited by common air conditioning. True air conditioning with cooling below the dewpoint and reheat are not necessarily used. Air velocity is determined for the air conditioning; and the room is known to have positive pressure with respect to other areas by a flow or pressure indicator. A particle class is not specified. However, these manufacturers have established a controlled environment and appropriate specifications for temperature, cleaning, and contamination controls are in place. For example,
filters should be replaced per schedule or as needed based on scheduled inspections. Any practices or factors from the following list that the manufacturer has deemed appropriate and elected to use should be specified and routinely performed or followed. Some additional factors that should be considered when planning and using a controlled environment include:

- proper attire and dressing anteroom;
- controlled use of, and entry into, controlled areas;
- prohibiting eating, drinking, smoking, or gum chewing;
- preventing use of lead pencils;
- regulating the storage of glassware and containers;
- preventing or controlling the cutting, tearing or storage of cardboard, debris, etc.;
- cleaning the room and production equipment per written procedure;
- the original design and cleaning of work surfaces and chairs;
- selecting correct furniture and eliminating all nonessential equipment;
- controlling room air quality (amount of particulates, pressure, velocity, and exchange rate);
- eliminating electrostatic charges by controlling work surface composition or grounding;
- ensuring cleanliness of raw materials, components and tools;
- controlling the purity, sterility, and non-pyrogenicity of process water; and
- maintaining prefilters, HEPA filters, and electrostatic precipitators.

Also see at the end of this chapter the procedure, "Clean Room and Work Station Procedure," which covers work practices, dress codes, and hygiene for employees working in clean rooms or at laminar-flow benches.

Monitoring

An appropriate system for regular monitoring should be established and maintained for each of these factors to be controlled for a given operation. This will ensure that equipment is performing properly and that the quality of the environment is within specifications. When a particle count Class is specified, monitoring of airborne particulates is usually done with an air sampler. Monitoring of work surfaces for microbes [colony forming units] may be done with surface contact plates or settling plates. However, settling plates should not be used for monitoring when horizontal laminar air flow is used as they are ineffective for this type of flow.

All sampling should be done per written procedure, and the data should be recorded. Further, periodic inspections of environmental controls and documentation of the inspections are required by the QS regulation. The inspection checkoff form or other record should be kept simple.

CONTAMINATION CONTROL

The QS regulation requires in 820.70(e) that every manufacturer establish and maintain procedures to prevent contamination of product or equipment. These process specifications are established by the manufacturer to ensure that finished devices will meet the company's quality claims. Typical device examples are: in vitro devices that are not contaminated with microbes, detergents or rodenticides; circuits that are not contaminated with flux; implants that are not contaminated with body oils and certain implants that are not contaminated with pyrogens. Pyrogens are substances that cause fever in humans, and they arise primarily from cellular debris of gram-negative bacteria. Certain implants such as orthopedic implants are not required or expected to be pyrogen free. Other devices are required to be nonpyrogenic including: transfusion and infusion assemblies, devices that come in contact with circulating blood or cerebrospinal fluid, intraocular lenses and the surgical instruments used in their implantation, and any device labeled as "nonpyrogenic". Manufacturers should carefully control the environment in which such devices are manufactured and processed to minimize contamination with bacteria or establish a procedure for cleaning the devices.

If necessary for the device to meet company product specifications or labeling claims, cleaning procedures and schedules to meet the requirements of section 820.70 may need to be written. Each operation should be analyzed in order to write an appropriate procedure or determine that one is not needed. For example, written procedures are usually not required for cleaning floors and work benches in areas where non-sterile and non-growth promoting components or devices are processed and packaged. An example of a procedure and schedule for cleaning an aseptic filling room is exhibited at the end of this chapter. Records related to facilities, the environment and personnel practices need to be kept simple as shown by this example. Note that the schedule and record of cleaning are both on page 4 of the procedure. The record of cleaning may be a checkmark, initial, or signature. Where a checkmark is used for repetitive work, companies commonly require that the person's name be on the record at least once. The schedule for cleaning may be posted or filed as long as it is in a convenient location. As appropriate, manufacturers may use this procedure as is, modify it, or use it as a guide to develop
a procedure to meet specific needs.

**Personnel Sanitation Practices**

Adequate bathroom, dressing, storage, and waste facilities should be provided, as appropriate, for personnel to maintain the needed level of cleanliness [820.70(d)]. Such facilities should be maintained on a regularly scheduled basis. Where necessary, such as in a clean room, special clothing and an area to don and store the garments should be provided. Clean room clothing is not be worn into uncontrolled rooms or outside the facility.

**Prevent Contamination by Hazardous Substances**

If rodenticides, insecticides, or other hazardous substances are used, written procedures to limit their use or for their removal from work surfaces and devices should be established to prevent any adverse affect on the manufacturing process or the device [820.70(e)].

**Personal Practices**

If eating, drinking, or smoking could have an adverse affect on the devices' fitness for use, manufacturing procedures should include instructions on how to avoid such adverse effects [820.70(d)]. For example, these activities could be confined to specially designated areas such as a lunch room or employees lounge. Directions and containers or equipment should be provided for timely and safe disposal of trash, by-products, effluents and other refuse.

**EXHIBITS**

Reprinted on the following pages are two examples of procedures that may be used to comply with the cleaning or contamination control requirements of the QS regulation. Both of these procedures deal with sensitive areas of the plant: clean room and aseptic filling rooms. Therefore, these are more comprehensive than is normally needed for general plant cleaning.

Note that these procedures follow good labeling practices in that the tasks or rules are broken into numbered steps; and only one or two activities or rules are included in each step. Thus, the directions or rules are easy to read, remember, and execute or obey.

**Clean Room and Work Station Procedure**

This procedure is divided into general requirements, non-laminar airflow clean rooms, and workstations, laminar airflow clean rooms and workstations, and clean room personnel rules. The first part of this procedure contains useful information for any area of a plant were moderate control is needed to reduce particulate contamination. The level of control needed increases as the procedure goes from non-laminar airflow to laminar airflow. The final section contains additional requirements for personnel working in a clean room.

**Cleaning Procedure for the Aseptic Filling Room**

This is a standard operating procedure used by personnel that are charged with cleaning an aseptic filling area and not for personnel that generally work in this area. This cleaning procedure is divided into two sections, daily and weekly tasks, thus giving personnel guidance on when, as well as, how to perform these tasks. Please note that many manufacturers will alternate the germicide in their cleaning solution to minimize the likelihood of resistant organisms developing. There are two items of interest in this procedure that should help to minimize entering and exiting this area: the equipment list at the beginning, and the maintenance information at the end. The equipment list is important because it alerts personnel to obtain the proper equipment before beginning work. The maintenance procedures allow the personnel to perform maintenance tasks without calling in a special crew or having to exit and re-enter the room unnecessarily.
A. General Requirements

1. No eating, drinking, smoking, or chewing gum.

2. Specified garments must be worn when entering and inside the clean area. These shall be stored in the anteroom and not worn in non-clean areas.

3. Only approved clean room paper shall be allowed in the area.

4. Use only ballpoint pens (fine point preferred).

5. Rouge, lipstick, eye shadow, eyebrow pencil, mascara, and false eyelashes shall not be worn by any worker while in any clean area.

6. No cosmetics of any kind are to be applied or removed in the clean area.

7. Skin lotions or lanolin-base soaps are in the restrooms for employees to use to guard against flaking due to dry skin.

8. Solvent contact with the bare skin should be avoided, as most solvents will remove the natural skin oils and cause excessive skin flaking.

9. The use of paper or fabric towels is not recommended -- washrooms should have electrically powered, warm-air dryers.

10. Approved pliers, tweezers or lint-free gloves must be used to handle manufacturing materials, components, or finished devices.

11. Do not touch with gloves or finger cots any covered or uncovered part of the body, or any item or surface that has not been thoroughly cleaned.

12. All containers, racks, jigs, fixtures, and tools should be cleaned to the same level of cleanliness specified for the device being processed.

B. Non-laminar Airflow Clean rooms and Work Stations

1. Garments shall be pocket-less, lint-free coveralls, with snug fitting fasteners at the neck, wrist, and ankles.

2. Lint-free caps must be worn and must completely cover the hair and head except for the eyes, nose, mouth, and chin.

3. Shoes shall be cleaned and covered with a non-shedding boot-type cover or changed to approved clean room footwear. If special footwear is provided, it shall not be worn outside the clean room and dressing room.

4. Janitorial services shall be performed only by adequately trained and supervised personnel, each of whom must be properly garbed.

5. All equipment to be brought into the clean room shall be qualified for clean room use and first be thoroughly cleaned. Use only equipment that will minimize the generation of contaminants.

6. Traffic into and within the clean room shall be restricted to authorized and properly garbed personnel, and unnecessary movements by these personnel shall be minimized.

C. Laminar Airflow Clean Rooms and Work Stations

1. Garments may vary with the operation being performed, but the minimum garment shall be a pocket-less, lint-free smock which
extends to at least 15 inches below the work surface. The collar and cuffs shall have fasteners.

2. Head covering shall be worn, and shall completely cover the hair. If the operation requires the wearer to lean over the work, or move into the airstream between the filter bank and the work piece, the front, sides, and rear neck areas of the head shall also be covered.

3. Shoe covers are not necessary for vertical or horizontal laminar airflow facilities except when the work is being performed less than 24 inches from the floor.

4. A face mask may be needed if an operator has a cold, or if the nose and mouth must be brought very close to the work piece for work on miniature components or devices. Check with your supervisor for instructions.

D. Clean Room Personnel Rules

Personnel will be asked to cooperate in maintaining a low contaminant emission rate by observing the following rules.

1. Bathe at night, instead of in the morning, to allow the build-up of normal body oils which reduces skin shedding. Also, use skin lotions.

2. Wear clean, unstarched, low-shedding garments.

3. Where appropriate, shave daily and be clean shaven or wear appropriate hair covering.

4. Avoid touching, rubbing, and scratching exposed areas of the body.

5. Exercise extra care to rid the hands of normal residue from home duties such as starching, baking, plastering, wallpapering, painting, concrete work, carpentering or other particulate generating activity.

6. Request duty outside the or away from the clean room area when you have a cold or other viral or bacterial infection.
(should be equipped with a HEPA filter on the exhaust air port to filter the exhaust air)

5. Sponge mops with replaceable sterile heads

6. Mop buckets

7. Stainless-steel sponges

8. Powder free latex surgical gloves, sterile

9. Head and shoe covers, sterile

10. Face masks and gowns, sterile

11. Stainless-steel cart

12. Sprayer

13. Trash can plastic liners

14. Stepladder

**DAILY CLEANING REQUIREMENTS:**

**CAUTION:** Be careful when using stepladder and when walking in wet areas. USE EXTREME CARE WHEN CLEANING ELECTRICAL FIXTURES AND OUTLETS. USE DAMP (NOT WET) CLOTH TO WIPE ELECTRICAL ITEMS.

**A. Gowning Room:**

Shoe and head covers are required in this area. Begin all cleaning at the top and finish at the bottom of any equipment or surface to be cleaned.

1. Empty trash containers and replace plastic liners.

2. Replenish stock of shoe covers, masks, head covers, gowns, gloves and put into proper areas.

3. Fill dispenser with 0.45 u filtered 70% Isopropyl alcohol.


5. Fill a stainless-steel basin with cleaning solution and begin wiping in this order: the boot box; stool; wash station; top and outsides of all cabinets; counter tops; and the tops of the trash containers.

6. Remove excess debris and wet mop the floor with cleaning solution.

7. Fill sprayer with cleaning solution and wet the floor; allow it to air dry.

8. Gown according to gowning procedures and go into the filling area (SOP G014).

**B. Filling Room:**
1. Move any remaining products (devices) to appropriate areas as directed by your supervisor.

2. Empty all trash containers and replace liners.

3. Remove particulate matter from ledges, cabinets and external surfaces of laminar-flow benches with a wiping cloth and cleaning solution.

4. Perform general cleaning and organization of shelves.

5. Remove debris and wet mop the floor with cleaning solution.

6. Spray the entire floor in the filling room with cleaning solution, using the provided sprayer. Allow the floor to air dry.

**WEEKLY CLEANING REQUIREMENTS:**

All daily cleaning requirements are included in the weekly cleaning requirements. The additions to the weekly cleaning are ceilings, walls, and the internal work surfaces of the laminar-flow work benches. Rodac™ plate measurements are taken after cleaning and before the next production shift.

**A. Gowning Room:**

1. Use only one entrance and one exit when cleaning. The cleaning direction will flow from entrance to exit.

2. Remove all non-essential equipment from the room and clean it. Return the equipment after the entire area is cleaned.

3. Begin cleaning the room by wiping the entire ceiling area with the cleaning solution.

   Frequent changes of the cleaning solution and the wiping cloths are needed for effective cleaning of large areas such as the ceilings and walls. Make new solution and change wiping cloths when dirty.

   1. Clean air vents, lighting fixtures, and sprinkler heads.

   2. Clean the walls next, starting at the top and cleaning toward the floor.

   3. When the ceilings and walls are cleaned, follow steps 1, 2, 3 and 5 of the Daily Cleaning Requirements for the gowning room.

   4. Remove debris and wet mop the floor with cleaning solution.

   5. Fill the sprayer with cleaning solution and wet the floor. Allow to air dry.

   5. Gown according to procedure and go into the Filling room (SOP G014).

**B. Filling Room:**

1. Follow steps 1, 2, 3 and 4 of Daily Cleaning Requirements for Filling Room.

2. Begin cleaning operation by wiping the entire ceiling area with cleaning solution. Make new cleaning solution and change wiping cloth when visibly dirty.
3. Clean air vents, ultraviolet and fluorescent lighting fixtures and sprinkler heads.

4. Clean the ultraviolet bulb since any oil or dust on the bulb drastically reduces its germicidal properties.

5. Clean the walls next, starting at the top and cleaning toward the floor. Make new cleaning solution, and change wiping cloth when dirty.

6. Empty all shelves and wipe with the cleaning solution. Wipe the removed materials and put them back onto the cleaned shelf.

7. Wipe all cabinets and equipment with the cleaning solution from top to bottom.

8. Wipe all ledges and surfaces with the cleaning solution.

9. Pay particular attention to the laminar-flow workbenches because the cleaning operation should start in the internal work surface of the hood as it is the cleanest area.

Use a fresh wiping cloth and cleaning solution for the internal work surfaces. Do not use the same cloth or solution which was used for the external cleaning. Discard solution and wiping cloths after cleaning each hood.

1. First, switch off the laminar-flow hood, then clean all outside surfaces from top of hood to bottom stand. Discard cleaning cloth.

2. Second, clean all internal work surfaces with a new cleaning cloth in this order:
   a. Air diffuser screen
   b. Workbench top.
   c. Plexiglas sides
   d. Light covers

3. Clean the floors. Scrub stains or spills first, with stainless-steel sponges, to loosen debris. Use the sponge mop to clean the loosened debris. Fill the sprayer with cleaning solution and wet the entire floor area. Allow to air dry. Rodac™ plate measurements are made after cleaning and before the next production shift.

4. Complete the documentation ledger and sign it. See Attachment A.

C. Maintenance of Cleaning Equipment After Daily and Weekly Cleaning:

1. Use the same solution as used for general cleaning.

2. Wipe stepladder from top to bottom, in that order, and put it into storage cabinet.

3. Wipe stainless-steel basins and pails with cleaning solution, allow to air dry, and put into storage cabinet.

4. Rinse mops and buckets with cleaning solution. Do not leave dirty solution in buckets or vacuum cleaner.

5. Rinse sponge mops with warm water. If mop head needs replacing, replace it and put mop into storage cabinet.
6. Wipe stainless-steel cart with cleaning solution and put into storage cabinet.

7. Rinse sprayer with cleaning solution and put into storage cabinet.


9. Autoclave mop heads and buckets per procedure GAC 09.

<table>
<thead>
<tr>
<th>ASEPtic FiLL DEPARTMENT CLEANING RECORD Week of</th>
<th>AREA</th>
<th>ITEM</th>
<th>SUN</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THU</th>
<th>FRI</th>
<th>SAT</th>
<th>WKLY</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOWNING ROOM</td>
<td>Empty waste containers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remove dirty uniforms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wipe ceilings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clean UV lights</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wipe walls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clean floors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FILL ROOM</td>
<td>Empty waste containers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Straighten shelves</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wipe ceilings, walls &amp; ledges</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clean UV lights</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clean floors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIR LOCKS</td>
<td>Wipe ceiling &amp; walls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clean floors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLEAN FILL RM</td>
<td>Empty waste containers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wipe ceilings &amp; walls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clean floors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POOLING AREA</td>
<td>Empty waste containers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wipe ceilings, walls &amp; ledges</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean UV lights</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clean floors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Indicate task completed each day by a check mark in appropriate box. Shift Supervisor: _____________________________

Updated 1/1/1997
7. Equipment and Calibration

INTRODUCTION
EQUIPMENT GMP CONTROLS
  Maintenance
  Records
MANUFACTURING MATERIALS
  Analyze Use
  Control Use
AUTOMATED PRODUCTION AND QA SYSTEMS
  Software Validation Guidances
  Employee Responsibility and Training
  Formal Development of Software
  Commercial Software and Equipment
  Validation of Automated Equipment and Processes
  Automated Data Collection and Processing
  Equipment Controls and Audits
MEASURING EQUIPMENT CALIBRATION
  Calibration Requirements Equipment Selection
  Procedures
  Management of Metrology
  Calibration Records
  Schedules
  Standards
  Calibration Environment

AUDIT OF CALIBRATION SYSTEM
INTEGRATING MEASUREMENTS INTO THE QA SYSTEM
EXHIBITS
  P.C. Board Cleaning
  Calibration Procedures for Mechanical Measuring Tools

INTRODUCTION
The Quality System (QS) regulation requires that each manufacturer develop, conduct, control, and monitor production processes to ensure that the end device conforms to its specifications [820.70]. All equipment used to
manufacture a device shall be appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use [820.70(g)]. The degree of maintenance on equipment and the frequency of calibration of measuring equipment will depend upon the type of equipment, frequency of use, and importance in the manufacturing process. Where deviations from device specifications could occur as the result of manufacturing processes, the manufacturer shall establish and maintain process control procedures. This chapter addresses the steps necessary to ensure that manufacturing equipment continuously operates within the parameters necessary to produce a product that meets specifications.

**EQUIPMENT GMP CONTROLS**

The selection, purchase, and installation of the most appropriate manufacturing equipment is important to successfully manufacture a medical device to specifications. After this manufacturing equipment has been installed and placed in operation, it shall be maintained. This includes the periodic inspection, adjustment, cleaning, and other maintenance of this equipment to insure that product specifications continue to be met [820.70(g)(1), (2) and (3)]. If the manufacturing equipment used in production includes computers or an automated data processing system, the manufacturer shall validate the software for its intended use and the software changes using an established protocol [820.70(i)]. In addition the manufacturer is responsible for ensuring the establishment of routine calibration [820.72], inspection, and maintenance on all of their inspection, measuring, and test equipment so this equipment will be suitable for its intended use(s).

Equally important to the purchasing and maintenance of manufacturing equipment is the adequate training of personnel so they are able to operate the equipment correctly [820.25(b) and 820.70(d)]. This training shall be documented. Included in adequate personnel training is the establishment and maintenance of requirements for health, cleanliness, personal practices, and clothing of employees when contact between these people and the product or the environment could reasonably be expected to adversely effect the finished product quality [820.70(d)].

**Maintenance**

Device manufacturers shall establish schedules to maintain, clean, and adjust equipment used in the manufacture of medical devices where failure to do so could have an adverse effect on the equipment's operation and hence the device. For example, failure to maintain, clean, and adjust a sealing and/or packaging machine used for primary packaging of sterile devices will eventually result in defective packages and thus nonsterile products.

A manufacturer should determine if the equipment requires maintenance and apply the appropriate parts of the GMP requirements for equipment. The user usually can determine if specific equipment requires maintenance by reviewing the equipment operations and maintenance manuals usually supplied by the equipment manufacturer. Typically, a manufacturer will maintain equipment simply because it prolongs equipment life and minimizes the need for major service.

If it is necessary to maintain, clean, or adjust equipment, the manufacturer should:

- have a written schedule for performing these activities;
- where adjustment is necessary to maintain proper operation, post the inherent limitations and allowable tolerances of the equipment or make these readily available to personnel responsible for making the adjustments;
● document the maintenance activities including the date and individual(s) performing the maintenance activity and the date and individual(s) conducting the inspections;

● have procedures for conducting periodic inspections to assure adherence to maintenance schedules; and,

● audit the activities and document the inspection.

Records

Manufacturers may find it helpful to establish and maintain maintenance procedures for manufacturing equipment in order to ensure meeting the manufacturing specifications. These procedures should include adjustment and cleaning, as well as other equipment maintenance. Documentation should be kept on maintenance activities including: the activity performed, the date, and the individual providing the maintenance [820.70(g)(1)]. An example of an operation and maintenance procedure, "P.C. Board Cleaning," is exhibited at the end of this chapter. Maintenance records and schedules are not needed for equipment such as lathes, presses, grinders, etc., that are used in a machine shop and maintained by skilled employees on a daily basis. Automated machining equipment will require maintenance schedules.

MANUFACTURING MATERIALS

The proper or optimum operation of manufacturing equipment often requires the use of lubricants and other manufacturing materials. The QS regulation defines "manufacturing material" as any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer [820.3(p)]. Manufacturing materials are often used with equipment. Manufacturing materials include, but are not limited to: mold release compounds; cleaning agents; lubricating oils; and other substances used to facilitate manufacturing. If any of these materials has an adverse effect on the finished device, procedures shall be established and maintained for the removal or at least the reduction of these manufacturing materials to an amount that will not adversely affect the device's quality.

Manufacturing materials are specified, procured, inspected/tested, etc., the same as components [820.3(r), 820.50, and 820.80]. For details see Purchasing and Acceptance Activities, Chapter 10 of this manual.

Analyze Use

The use of manufacturing materials that may adversely affect the finished device should be carefully analyzed. Each process should be designed to use a minimum amount of adverse materials so as to reduce costs, reduce removal efforts, and increase the intrinsic safety of the device. Whether or not a manufacturing material has been removed or adequately limited may be determined by using either of the two general approaches below.

● The adverse material may be measured directly and compared to the process specification.

● If feasible, the component, in-process device, or finished device may be tested against its specification. If the item passes, it follows that the residue is not affecting the performance. The test specification should be appropriate for this method of evaluating residues and may need to include tests for toxicity, pyrogens, material compatibility, etc.
Control Use

Section 820.70(h) requires a written procedure for the use and removal of manufacturing materials that can have an adverse effect on devices. Usually, the procedure used for routine cleaning of the device and its assemblies can be used for this purpose. If so, a special procedure is not necessary. However, when residues from agents such as ethylene oxide should be reduced, special instructions usually are necessary.

When manufacturing materials such as oils, mold-release compounds, gases, cleaning agents, etc., are used on or in equipment, manufacturers should:

- provide written procedures for the use and removal of materials; and
- remove the material or limit it to a safe amount;
- document the removal.

Where a manufacturing material residue is not or cannot be made safe for everyone such as for sensitized individuals, the manufacture should meet limits set by regulation, standards, guidance, etc. When appropriate, a caution label should be used to advise sensitized or atopic individuals about the residue.

A sample procedure, "P.C. Board Cleaning", covering equipment used for removing adverse manufacturing materials (flux and debris) is exhibited at the end of this chapter. This procedure covers the removal of flux, finger oils, debris, etc., from printed circuit (PC) boards. In some cases, flux is an adverse manufacturing material.

AUTOMATED PRODUCTION AND QA SYSTEMS

The hardware system, software program, and general quality assurance system controls discussed below are essential in the automated manufacture of medical devices. The systematic validation of software and associated equipment will assure compliance with the QS regulation; and reduce confusion, increase employee morale, reduce costs, and improve quality. Further, proper validation will smooth the integration of automated production and quality assurance equipment into manufacturing operations.

Medical devices and the manufacturing processes used to produce them vary from the simple to the very complex. Thus, the QS regulation needs to be and is a flexible quality system. This flexibility is valuable as more device manufacturers move to automated production, test/inspection, and record-keeping systems.

Software Validation Guidances

The QS regulation requires in 820.70(i) that software programs be validated for their intended use according to an established protocol when computers are used as part of an automated production or a part of the quality system. Software used in automated production and quality systems consists of programs or codes that cause computerized equipment to perform desired tasks, plus operator manuals and instructions. FDA has drafted an information document, "Application of the Medical Device GMPs to Computerized Devices and Manufacturing Processes," which is reprinted in the Appendix. Also, a document entitled, "Reviewer Guidance For Computer Controlled Medical Devices Undergoing 510(k) Review," is available from DSMA. Both of these documents can be used with the QS regulation to help establish a software QA and validation program.

There are also standards, books, and articles that can be used for guidance. Military Specification MIL-S-52779A and the Institute of Electrical and Electronic Engineers (IEEE) "Standard for Software Quality Assurance Plan" (IEEE Std
Employee Responsibility and Training

The device manufacturer should identify individuals or departments responsible for software quality and clearly specify their responsibilities. These individuals and/or department personnel should have sufficient training, authority, responsibility, and freedom of action to specify and evaluate the design and use of software and associated equipment.

A manufacturer probably will experience problems if employees operating the automated system or inputting data do not have adequate background and/or training. Employees should have adequate knowledge of the system through both formal training and on-the-job experience. Those responsible for data input should be able to recognize data errors (820.25). The QS regulation requires that processes be controlled (820.70). Thus, automated systems should be designed [820.70(a)] and employees trained (820.25) to help prevent inaccurate data input or adjustments. This requirement can be accomplished by the aforementioned training and by software controls. Where practical, software programs should have built-in error controls such as prompts, alpha-only fields, numeric only fields, length limits, range limits, and sign (± or −) control to help eliminate mistakes during data entry. These error-control or human-factors requirements, as appropriate, should be part of the specifications for software being developed or purchased.

Formal Development of Software

Manufacturers that develop their own process control software shall follow the design controls in 820.30 and document each step of the development. The software should be appropriately structured and documented so that any future changes can be accomplished, even by a different programmer, with a minimum of difficulty and maximum reliability.

To validate software, it should be:

- structured, documented and verified as it is developed;
- checked to make sure that it meets specifications;
- adequately tested with the assigned hardware systems; and
- operated under varied conditions by the intended operators or persons of like training to assure that it will perform consistently and correctly.

Each module or routine of the program should be verified to make sure it performs the specified function. The main core of the program should be checked to make certain that all parameters are correctly initialized and that data is correctly transferred between the routines. The input-output routines should be checked for proper operation with the intended peripherals to the extent feasible at this stage of the development. The testing is performed with real or simulated input data. The input data should accurately represent the real data that will occur in the next phase of testing. This input data should include data at the boundaries of acceptability, i.e., limit testing. The test protocol, data and results should be documented. The documentation should be made available to the party, who will evaluate the software with the automated production or quality assurance equipment to be used in routine manufacturing.

The testing of the software with the actual medical device production or testing equipment should exercise program functions under expected production conditions. The testing should include the input of normal and abnormal (limited case) data to test program performance and error handling. The validation should assure that the software and associated equipment meet the company specifications. The test protocol, testing, results, and design review should be documented in the design history file. Procedures for use and maintenance of the equipment and acceptance of the
Commercial Software and Equipment

When an outside contractor is engaged to develop software, the device manufacturer should make sure that the contractor clearly understands the software requirements and translates them into documented specifications with sufficient objectivity that compliance can be measured. FDA recognizes that most of the validation may be done by the contractor, however, the device manufacturer is still responsible for the adequacy and the validation of the software for its intended use. Therefore, the contractor should be required to develop the software according to a quality system plan that includes validation.

When possible, the purchaser also should conduct pre-award audits to verify adequacy of the contractor's quality system. Two key elements that should be checked are the contractor's test plans and system for controlling changes to documentation. Subsequent audits should be conducted as needed to verify that the contractor is complying with the quality system plan. The manufacturer who has custom software prepared and validated by a contractor should ensure the software program is running properly and producing correct results before using the program to produce medical devices for distribution.

Manufacturers who purchase commercial equipment with incorporated software should validate the software and associated equipment for the intended applications. If, however, the software has been validated by the developer and proven through use, the purchaser need not test it as comprehensively as new software. For example, automated production and test equipment that is controlled by software can usually be validated through use of a "dummy" device. This "dummy" device should exercise functions and decisions in normal and limit-case situations that may reasonably be expected during production. In some cases, suppliers provide test programs that may be used to assure that the equipment will appropriately and accurately perform all intended functions before it is used for routine production.

Validation of Automated Equipment and Processes

Validated, automated machine tools such as lathes, printed-circuit drills, and component inserters usually can be monitored and maintained by conducting a first and last-piece inspection of representative product lots. The record of this activity may be noted on the routine quality control or production records for the machine. Validation of complex microprocessor-controlled equipment, such as sterilizers or to verify satisfactory operation is generally a more extensive activity than the validation of machine tools. Typically, verification should be done by using calibrated measurement instruments to check the actual parameters achieved during trial runs, and comparing these measurements with the set points and data outputs of the automated system. In all cases, under the QS regulation the user is responsible for:

- assuring the adequacy of automated equipment and software;
- verifying that all intended functions will be correctly and reliably performed; and
- maintaining appropriate records.

Validation records [820.70(i)] for software and automated equipment can be maintained by the user in the design history file [820.30(j)], the device history record [820.184], or the quality system record [820.186], depending on what works best for the manufacturer. Specifications for the hardware and software including directions for their use, if any, shall be included or referenced in the device master record [820.181]. The device master record [820.3(j)], as explained in Chapter 8, is a compilation of records containing procedures and specifications for a finished device. The device master record (DMR) contains or references the records covering the use of the equipment and the output product are documented in the device master record. Any serious deficiencies should be corrected.
specifications of the output product. Upon request, these records shall be made available to FDA investigators for review and copying during their audit [820.180] of the manufacturer's GMP system.

All changes to software programs shall be formally reviewed and approved before implementation [820.30, 820.70 and 820.40]. Because changes in one part of software can affect other parts of software, adequate consideration should be given to side-effects of these changes. Such changes are much easier to make and evaluate when the original software is appropriately structured and thoroughly documented.

**Automated Data Collection and Processing**

In addition to aiding the production of devices, computers may be used to collect and maintain quality control and production records. These records are called the device history record in the QS regulation. A device history record [820.3(i)] is a compilation of records containing the production history of a finished device. When design history files, device history records, device master records, or quality system records are maintained by computer, appropriate controls should be used to assure that data is entered accurately, changes are instituted only by authorized personnel, and records are secure. Hard copy or alternative systems such as backups [820.180], duplicates, tapes, or microfilm should also be used to avoid losing records as a result of inadvertent erasure or other catastrophe. As appropriate, access to records and data bases should be restricted to designated individuals.

The increased use of computers and related input/output peripherals has affected FDA policy regarding GMP signature requirements. In response to the use of electronic technology, FDA has issued an advisory opinion stating that magnetically coded badges or other computer-compatible identifiers may be used in lieu of signatures as long as there are adequate controls to prevent inaccurate data input. If coded badges and the like are not controlled (i.e., not restricted to designated employees), they will not meet the applicable GMP requirements.

Manufacturers may wish to keep appropriate records such as device master records and complaint files at central or corporate offices. If the overall data handling system is controlled as stated above, manufacturers may maintain appropriate quality system records at central locations if they can transmit these records to the manufacturing establishment by computer plus modem, or other high speed data transfer system.

**Equipment Controls and Audits**

Automated equipment and any peripheral equipment requiring maintenance and/or calibration shall be included in a formal calibration and maintenance program [820.72]. Also, environmental factors such as temperature, humidity, contamination, static electricity, magnetic fields, and power-supply fluctuations can adversely affect automated equipment and data storage equipment such as magnetic discs, tapes, optical systems, etc. Consequently, necessary precautions, environmental controls, and maintenance programs [820.70] shall be implemented to prevent adverse effects on the equipment and stored data.

During the quality system audit [820.22], manufacturers shall audit the use and control of their automated production and quality systems. The audit should include software and equipment maintenance procedures and records, and should evaluate the adequacy of security measures, change controls, and other controls necessary to maintain software quality and proper performance of associated equipment. The audit shall be documented, important results reviewed with management, and corrective action taken as appropriate.

**MEASURING EQUIPMENT CALIBRATION**
The QS regulation is intended to help assure that devices will be safe, effective, and in compliance with the FD&C Act. To support this goal, each medical device manufacturer should develop and implement a quality system that assures, with a high degree of confidence, that all finished devices meet the company's device master record specifications. These specifications should, in turn, reflect the company quality claims. Section 501(c) of the FD&C Act states a device shall be deemed to be adulterated if its strength differs from, or its purity or quality falls below, that which it purports (claims). Such assurance is obtained by many activities including the measurement of component, device, and process parameters during design and production. These measurements shall be made with appropriate and calibrated equipment as required by 820.72.

Each manufacturer should assure that production equipment and quality assurance measurement equipment, including mechanical, electronic, automated, chemical, or other equipment, are:

- suitable for the intended use in the design, manufacture, and testing of components, in-process devices and finished devices;
- capable of producing valid results;
- operated by trained employees; and
- properly calibrated versus a suitable standard.

To succeed, the quality system shall include a calibration program that is at least as stringent as that required by the QS regulation (820.72). The intent of the GMP calibration requirements is to assure adequate and continuous performance of measurement equipment with respect to accuracy, precision, etc. The calibration program implemented by a company may be as simple or as sophisticated as required for the measurements to be made. Some instruments need only be checked to see that their performance is within specified limits, while others may require extensive calibration to a specification.

Manufacturers should determine which measurements are necessary to assure that finished devices meet approved device master record specifications, and assure these measuring instruments are included in a calibration program. Measurement equipment should be identified by label, tag, color code, etc., when located in the same areas as instruments that are not part of the calibration system. Identification can assure that proper equipment is employed to verify and determine compliance to specification of a device component, in-process device, or finished device.

Sometimes equipment used only for monitoring a parameter need not be calibrated but should be identified (e.g., for monitoring). A monitoring function might be to indicate if a voltage or other parameter exists, but the exact value is not important.

**Calibration Requirements**

The QS regulation requires in section 820.72(b) that equipment be calibrated according to written procedures that include specific directions and limits for accuracy and precision. Figure 5.1 illustrates bias, precision, and accuracy.

Precision has no unit of measure and only indicates a relative degree of repeatability, i.e., how closely the values within a series of replicate measurements agree with each other. Repeatability is the result of resolution and stability.

Bias is a measure of how closely the mean value in a series of replicate measurements approaches the true value. The
mean value is that number attained by dividing the sum of the individual values in a series by the total number of individual values.

Accuracy is the measure of an instrument’s capability to approach a true or absolute value. Accuracy is a function of precision and bias. Because different manufacturers have different accuracy requirements, each manufacturer should decide the level of accuracy required for each measurement and provide equipment to achieve that accuracy.

Figure 5.1 Bias, Precision and Accuracy

Proper and periodic calibration will assure that the selected equipment continues to have the desired accuracy. GMP calibration requirements are:

- routine calibration according to written procedures;
- documentation of the calibration of each piece of equipment requiring calibration;
specification of accuracy and precision limits;

training of calibration personnel;

use of standards traceable to the National Institute of Standards and Technology (NIST), other recognizable standards, or when necessary, in-house standards; and

provisions for remedial action to evaluate whether there was any adverse effect on the device's quality.

Remedial action includes recalibration and evaluation of the impact of out-of-tolerance measurements:

- on the device design or process validation parameters or data;
- on the quality of existing components, in-process, or finished devices; and
- appropriate corrective action.

**Equipment Selection**

The manufacturer should establish and maintain procedures to ensure that purchased and otherwise received equipment and associated supplies conform to specified requirements (820.50). The purchase of stable and accurate measuring equipment can reduce the frequency of calibration and increase confidence in the company's metrology program. Where economically feasible, equipment with more accuracy than needed for various measurements can be used longer without recalibration than equipment that marginally meets the desired accuracy requirements. Delicate instruments, however, that are "pushing the state-of-the-art" should not be used for routine measurements unless no other approach is feasible.

**Procedures**

There are a number of sources of information from which calibration procedures can be developed. Instrumentation manufacturers often include calibration instructions with their instruction manuals. Although these instructions alone are not adequate to meet the QS requirements for a calibration procedure, they usually can be used for the actual calibration process. In some cases, voluntary standards exist such as those by the American Society for Testing and Materials (ASTM), the American National Standards Institute (ANSI), and the Institute of Electrical and Electronic Engineers (IEEE).

Information contained in calibration procedures should be adequate to enable qualified personnel to properly perform the calibrations. An example of a calibration procedure for mechanical measuring tools appears at the end of this chapter.

A typical equipment calibration procedure includes:

- purpose and scope;
- frequency of calibration;
- equipment and standards required;
- limits for accuracy and precision;
- preliminary examinations and operations;
- calibration process description;
- remedial action for product; and
Management of Metrology

Managers and administrators should understand the scope, significance, and complexity of a metrology program in order to effectively administer it.

The selection and training of competent calibration personnel is an important consideration in establishing an effective metrology program. Personnel involved in calibration should ideally possess the following qualities:

- technical education and experience in the area of job assignment;
- basic knowledge of metrology and calibration concepts;
- an understanding of basic principles of measurement disciplines, data processing steps, and acceptance requirements;
- knowledge of the overall calibration program;
- ability to follow instructions regarding the maintenance and use of measurement equipment and standards; and
- mental attitude which results in safe, careful, and exacting execution of his or her duties.

Calibration Records

Calibration of each piece of equipment shall be documented to include:

- equipment identification,
- the calibration date,
- the calibrator, and
- the date the next calibration is due.

Many manufacturers use a system where each device has a decal or tag which contains the date of calibration, by whom calibrated, and date the next calibration is due. Examples of such decals are shown below.

These decals are examples of the types commonly used to identify the status of measuring instruments and tools. They are available as catalog items or a manufacturer may use its own artwork to purchase decals with specialized wording.
Calibration information is entered onto cards or forms, one for each piece of equipment, or entered into a computerized data system. Most data systems include the calibration date, by whom calibrated, date recalibration is due, the reason for the calibration, comments, address of the manufacturer and calibration laboratory, equipment specifications, serial number, use, etc. An example of a typical card used to record calibration information follows.

Typical calibration decals have a write-on surface. A tough paper or cloth stock and a pressure sensitive adhesive are used for easy application and removal of the decal. “Due” is the blank for the date when recalibration is due.

Calibration Identification Number or its equivalent is usually the minimum information that may be on equipment. This information allows the manufacturer to read by finding the associated calibration record/card/file.

Measuring equipment that is not calibrated or otherwise unsuitable for use should be placed in a quarantine area or labeled with a "calibration void" decal.

A seal or protective cover for exposed, recessed calibration controls on instruments. The calibration control cannot be adjusted without breaking the seal or removing the instrument case.

A decal to be applied to measurement or monitoring instruments not intended for use in determining conformance to device master record specifications with respect to testing, manufacturing, environmental control, etc.

Calibration information is entered onto cards or forms, or for
Schedules

Measuring instruments should be calibrated at periodic intervals established on the basis of stability, purpose, and degree of usage of the equipment. Intervals between calibrations should be shortened as required to assure prescribed accuracy as evidenced by the results of preceding calibrations. Intervals should be lengthened only when the results of previous calibrations indicate that such action will not adversely affect the accuracy of the system, i.e., the quality of the finished product.
A manufacturer should use a suitable method to remind employees that recalibration is due. For small manufacturers, calibration decals on the measuring equipment may be sufficient because recalibration can be tracked by scanning the decals for the recalibration date. For other manufacturers, a computerized system, calibration cycle cards, tickler file, or the like may be used. Calibration cycle cards are maintained in a 12-month (12-section) tickler file. There is one card per item of measuring equipment. The cards in the section of the file for the current month are pulled and all of the equipment listed is calibrated. For example, in a 6-month calibration cycle, when an instrument is calibrated in May, the card is moved from the May section to the November section of the file. When the file is checked in November, the cycle card will be there to remind the manufacturer that calibration is due. The process is repeated until an event such as instrument wear-out occurs and the respective cycle card is removed from the file.

Cycle cards are used where a manufacturer has many instruments to be calibrated. It would be rather difficult to keep track of the calibration of a large number of instruments by reviewing calibration record cards or scanning the decal on each instrument. It is easier to use a cycle card file. A cycle card file or equivalent also should be used if the calibration records are filed by type of instrument or manufacturer rather than due date. A typical cycle card follows. The "calibration card number" blank refers to the calibration record card for the same item of equipment.

<table>
<thead>
<tr>
<th>CALIBRATION CYCLE CARD FORM NO. 5-15</th>
</tr>
</thead>
<tbody>
<tr>
<td>MANUFACTURER: _</td>
</tr>
<tr>
<td>INSTRUMENT: _</td>
</tr>
<tr>
<td>MODEL NO. SERIAL NO. _</td>
</tr>
<tr>
<td>CALIBRATION INTERVAL: _</td>
</tr>
<tr>
<td>LOCATION OF EQUIPMENT: _</td>
</tr>
<tr>
<td>CALIBRATION CARD NO. _</td>
</tr>
</tbody>
</table>

Standards

Where practical, the QS regulation requires that standards used to calibrate equipment be traceable to the National Institute of Standards and Technology (NIST), or other recognized national or international standards. Traceability also can be achieved through a contract calibration laboratory which in turn uses NIST services.

The meaning of traceability to NIST is not always self-evident. Two general methods commonly used to establish and maintain traceability to NIST are:

- NIST calibration of standards or instruments: When this method is used, private standards are physically sent to NIST for calibration and returned.

- Standard Reference Materials (SRM's): NIST provides reference materials to be used in a user's calibration program. These SRM's are widely used in the chemical, biological, medical, and environmental fields.
Information can be obtained from the "Catalog of NIST Standard Reference Materials," available free from the National Institute of Standards and Technology, Office of Standard Reference Materials, Gaithersburg, MD 20899, phone: (301)975-2016.

When in-house standards are used, they should be fully described in the device master record or quality system record. Independent or in-house standards should be given appropriate care and maintenance and should be used according to a written procedure as is required for other calibration activities. FDA recommends that at least two in-house standards be maintained -- one for routine use and one for a back up.

**Calibration Environment**

As appropriate, environmental controls should be established and monitored to assure that measuring instruments are calibrated and used in an environment that will not adversely effect the accuracy required. Consideration should be given to the effects of temperature, humidity, vibration, and cleanliness when purchasing, using, calibrating, and storing instruments.

**AUDIT OF CALIBRATION SYSTEM**

The calibration program shall be included in the quality system audits required by the QS regulation. These audits should determine the continuing adequacy of the calibration program and assess compliance with the program.

Many manufacturers use contract calibration laboratories to calibrate their measurement and test equipment. If this is the case, FDA views the contract laboratory as an extension of the manufacturer's GMP program or quality system. Normally FDA does not inspect contract laboratory facilities, but it does expect the manufacturer to assess the contract lab to verify that proper procedures are being used. Generally, the manufacturer of the finished device is responsible for assuring the device is manufactured under an acceptable quality system.

When a medical device manufacturer uses a contract calibration laboratory, FDA expects the manufacturer to have evidence that the equipment was calibrated according to the GMP requirements. The device manufacturer can do this by:

- requiring and receiving certification that the equipment was calibrated under controlled conditions using traceable standards;
- maintaining an adequate calibration schedule;
- maintaining records of calibration; or
- periodically auditing the contractor to assure appropriate and adequate GMP procedures are being followed. For example, the contractor should have:
  - written calibration procedures;
  - records of calibration;
  - trained calibration personnel; and
  - standards traceable to NIST or other independent reproducible standards.
Certification notes and data should include accuracy of equipment when received by the lab to facilitate remedial action by the finished device manufacturer, if necessary. Certification should also include accuracy after calibration, standards used, and environmental conditions under which the equipment was calibrated. The certification should be signed and dated by a responsible employee of the contract lab.

If in-house standards are used by a contractor to calibrate device-related measuring equipment, these standards shall be documented, used, and maintained the same as other standards.

INTEGRATING MEASUREMENTS INTO THE QA SYSTEM

Proper and controlled calibration can contribute to overall quality by assuring that device design and process parameters are accurately measured and that unacceptable items are not accepted, and acceptable items are not rejected as a result of measurements. If the appropriate product-quality parameters are not checked, however, calibrated equipment will have little impact on assuring quality.

A good quality system shall include calibration activities. However, proper calibration will be of little use unless the applications of the measurement equipment are properly developed and qualified during the preproduction development of inspection test methods and procedures. As stated, effectiveness depends on the participation and influence of QA and production management at the preproduction stage. Calibration of equipment cannot correct poor design of products nor can it compensate for poor applications of equipment and techniques. It is the continued use of a complete, integrated quality system, which assures that safe and effective devices are produced.

EXHIBITS

Examples of calibration cards, decals, and cycle cards were presented above in the text. Examples of a device cleaning procedure and a calibration procedure follow. Manufacturers may use these as presented if they match the manufacturers operations; or may modify them to meet specific requirements.

P.C. Board Cleaning

This procedure covers the cleaning of printed circuit boards by using an automatic washer. The procedure covers operation, shut down, cleaning, and routine maintenance.

Calibration Procedures for Mechanical Measuring Tools

This is a calibration procedure for mechanical measuring tools. In actual use, the initial accuracy of each tool is checked using the procedure and is recorded. Thereafter, each tool is recalibrated (checked) versus the initial accuracy. Of course, the initial accuracy should meet or exceed the requirements of the measurements to be made with the tool. Precision is checked by making several measurements at various points on the tool's measuring face (surface).

TITLE: P.C. Board Cleaning NO: ______________________________

REV: ______________________________ Sheet: 1 of 2

DRAFT: __________________________ APP: ________________________ DATE: _______
1.0 PURPOSE: The purpose of this procedure is to document production operations performed on the XXXXXXX printed circuit board washer.

2.0 SCOPE: This procedure sequentially identifies all operations necessary to properly operate and maintain this equipment.

3.0 OPERATING PROCEDURES:

3.0.1 Switch the Exhaust Systems fan on.

3.0.2 Assure that the sump pump is on at the circuit breaker panel.

3.1 Turn the power switch to the "ON" position.

3.2 Push the main power "START" button (#21 on Control Panel Diagram).

3.3 Visually inspect all pump compartment and screen filters for debris - make sure they are clean before continuing.

3.4 Push the fill buttons on the rear control panel to fill the wash and rinse sections with water. Make sure all drain lines are closed. The incoming water will stop automatically when the tanks are filled to the correct levels.

3.4.1 Add 4 gallons XXXXXXX detergent to the wash tank.

3.5 Depress the center knob on the temperature controllers (#30 on control panel diagram) and turn clockwise until the red pointer indicates 60° (140°F) for the wash tank and 60° C (140°F) for the rinse tank.

3.6 Wait about 10 min. for water temperature to rise in the wash and rinse tanks. Wait until the red lights on the temperature controllers go off and the black needle aligns with the red pointer.

3.7 Push the START-STOP button (#25 on diagram) on for the conveyer.

3.7.1 Adjust the "SPEED CONTROL" (#27 on diagram) to the correct setting for the boards to be run. See the cleaning specifications for each family of boards for the set points.

3.8 Push the "START" button (#28 on diagram) on for the dryer cycle. NOTE: conveyer belt MUST be moving when dryer section is on or the equipment will be damaged.

3.9 Turn Photocell Switch (on Rear Panel) to the "Automatic" position.

4.0 SHUT DOWN PROCEDURES:

4.1 Push the dryer cycle "STOP" button for the Wash and Rinse sections (#29 on control panel).

4.2 Turn Photocell Switch (on Rear Panel) to the "OFF" position.
4.3 Push the conveyer "START - STOP" button (#25 on diagram) to stop the conveyer.

4.4 Pull the DRAIN buttons on the control panel for the wash and rinse sections. Using litmus paper, take a reading on the wash tank before draining it. IF the wash water has a reading of "10" or less drain it; otherwise, do not drain the wash tank. Always drain the rinse tank.

4.5 Pull the FILL buttons on the control panel for the wash and rinse sections to let water flush the equipment for five minutes. Using a soft cloth, wipe off any residue remaining on the equipment.

4.6 Pull the drain buttons on the control panel for the wash and rinse sections to let the water drain.

4.7 Remove the screen filter in the washer and remove any debris.

4.8 Wipe the exterior front section of the machine with a soft cloth.

4.9 Push the main power "STOP" button, (#33) to shut off the equipment.

5.0 MAINTENANCE:

5.1 Monthly

5.1.1 Lubricate the conveyer drive chain with high temperature grease.

5.1.2 Check the wear strips on the conveyer belt frame and replace if required. These are two white plastic strips located at the front of the equipment.

5.1.3 Check conveyer belt tightness - using a wire cutter and needle nose pliers, remove links to tighten if required.

5.2 Quarterly

5.2.1 Shut off power in main panel at rear of equipment.

5.2.2 Lubricate pump motor ball bearing using standard bearing grease.

5.2.3 Lubricate flange bearings on conveyer shafts with bearing grease.

5.2.4 Check all wiring for loose connections and tighten if necessary.

5.2.5 Check all heater contacts - replace worn contacts.
PURPOSE: This procedure establishes a standard method for the calibration and maintenance of mechanical measuring tools such as micrometers, calipers, etc.

SCOPE: All measuring tools used to set specifications or measure conformance to specifications, such as micrometers, calipers, etc., will be included in the calibration program. Each tool will be assigned a number and checked every six months for accuracy. If you suspect a tool is damaged or out of calibration, it should be removed from service and brought to the Quality Control Lab (QC) for checking. To enter a tool in the program, take it to QC where a number will be assigned and initial accuracy checked and recorded.

PROCEDURE:

1. Each measuring tool shall be kept clean and maintained in a protective container. As needed, all threads and slides shall be lubricated with a fine tool oil to assure free movement.

2. The calibration shall be done by a comparison to standard gage blocks traceable to the National Institute of Standards and Technology standard with an accuracy 3 to 10 times greater than that of the measuring tool.

3. The comparisons shall be made at different points along the measuring range of the tool. The gage blocks used shall be picked at random to assure that the measuring tool is not checked at the same points on each calibration cycle. When a measurement is made, move the gage blocks from one side of the tool's measuring face to the other on an X/Y axis to assure no wear or taper exists on the measuring faces.

4. Measurement tools not intended for testing or manufacturing do not require calibration in accordance with the QS regulation. These tools should be kept out of manufacturing or labeled to avoid inadvertent use. Otherwise, they should be entered in this calibration program.

5. After calibration, the date of calibration and the next due date of calibration shall be recorded on the Calibration Form No. ______. Any adjustments and/or repairs to be recorded. The form is placed in the tickler file according to the next calibration date.

6. If a tool is found to be out of calibration, the QC lab will immediately pass the out-of-calibration information to the appropriate supervisor in the department where the tool is used. The Department and QC management will take appropriate remedial action for affected in-process or finished devices.

Updated 1/1/1997
8. Device Master Record

INTRODUCTION
Document For Intended Employees
Adequate Information
Preparation and Signatures
Location of Records
Record Retention

DEVICE MASTER RECORD CONTENTS
Device Specification
Specific Documents
Records for In Vitro Diagnostic Products

QUALITY SYSTEM RECORD DOCUMENTS

WRITTEN PROCEDURES
Developing Procedures
Content of Procedures

CHANGE CONTROL

EXHIBITS
Documents That May Appear in a Device Master Record
Device Master Record Index
Product Specification for a Portable Defibrillator
Zener Diode Specification
Label Example
Handle Assembly and Parts List
Cable Assembly and Parts List
Device Master Record Index for Amylase
Product Description
Amylase Diluent Solution
Filling Record - Liquid, Non Freeze Dried
Finished Product Release Form
Production Sample Card
INTRODUCTION

Device master record (DMR) is the term used in the Quality System (QS) regulation for all of the routine documentation required to manufacture devices that will consistently meet company requirements. Section 820.3(j) of the QS regulation defines device master record as a compilation of records containing the procedures and specifications for a finished device. The detailed requirements for device master records are contained in section 820.181, as well as throughout the regulation.

The definition for design output in 820.3(g) gives the basis and/or origin of the device master record for all Class II and III devices as follows:

Design output means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.

For some devices, many of the design output documents are the same as the device master record documents. Other device output information is used to create a DMR drawing such as for a test or an inspection procedure. Figure 6.1 shows the close relationship between design output and the device master record.

Section 820.181, Device Master Record, lists some typical documents in a DMR as follows:

The DMR for each type of device shall include, or refer to the location of, the following information:

(a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications;

(b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications;

(c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used;

(d) Packaging and labeling specifications, including methods and processes used; and

(e) Installation, maintenance, and servicing procedures and methods.

The definition for Design Output 820.3(g) and requirements for Design Output 820.30(d) do not apply to most Class I devices. Therefore, the requirements for the DMR for most Class I devices are in 820.181 Device Master Record. Of course, a manufacturer of Class I devices may use the design output sections of the GMP as guidance.
However, almost all sections of the QS regulation have requirements related to the device master record. The device master record contains specifications for the device, accessories, labeling, and packaging, and contains a full description of how to procure the components and manufacture the device including specifications for facilities, environment, and production equipment. In addition to the device specifications, a device master record contains documents that cover typical manufacturing activities such as:

- procurement,
- assembly,
- labeling,
- test and inspection,
- packaging, and
- where applicable, sterilization.

Note that the listed activities and records or documents are required to produce any product -- medical, industrial, or consumer. There is nothing special about device master records except the name!

Also, note that in common usage, the term "device master record" refers to the total record or any of its individual records. Therefore, the term is singular for the total record, singular for a single document, and plural for a group of single documents. The term also may refer to an original record or a copy of a record.
Device master records should be technically correct, contain and/or reflect the approved device and process designs, be under change control, contain the release or other control date, contain an approval signature, and be directed toward the intended user. These requirements are in the QS regulation because the device master record is the "beginning and end" of a product -- errors in the device master record will have a serious impact on the state-of-control of the manufacturing operation and may have a serious impact on the safety and performance of the device. The device master record should be accurate and complete because the essence of the QS regulation is a quality system based on designing a device to meet user needs, documenting the design and production procedures in the device master record and then producing a finished device that meets the device master record requirements. Thus, the device master record shall accurately reflect the device intended to be produced by a manufacturer.

**Document For Intended Employees**

The content, style, language, graphics, etc., of device master records should be directed toward the needs of the intended employees and, if the record is a specification or text for labeling, it should be directed toward users. A failure to consider the intended user leads to confusion and means that the company
has not achieved the state-of-control intended by the QS regulation. Therefore, applicable records should be directed toward the needs of procurement, processing, and test/inspection personnel, rather than the needs of drafting, technical services, or product development departments. Likewise, installation instructions should be directed to installers. Labeling is often prepared by the same employees that draft device master records; and, these employees should also be aware that labeling shall meet the needs of the user as directed by 21 CFR 809.10, 801.6 and 820.30.

In any manufacturing activity such as assembly, labeling, processing, testing, etc., achieving and maintaining a state-of-control is enhanced by appropriate personnel knowing:

- what task is to be done,
- how to do the task,
- who is to do the task,
- what task is being done, and
- what task was done and/or the results of the activity.

In order for employees to perform a job correctly, they should know exactly what is to be done and exactly how to do the work. Section 820.181 requires that what is done be documented in the device master record. The device master record also contains test and inspection procedures and data forms that are used to help determine and record what was done.

Documents that instruct people how to fabricate, assemble, mix, label, test, inspect, etc., or how to operate equipment should:

- be directed toward the needs of the employees who will be using them and not directed toward the drafts-person or designer;
- match the tools and equipment to be used;
- be correct, complete, and current; and
- depend on part numbers and basic drawings to transfer information rather than almost photographic type drawings.

If a component is changed, the representations on pictorial/photographic type drawings are no longer correct and may be very confusing to employees, particularly new employees.

The how-to-manufacture instructions should be adequate for use by the intended employees and correct for the intended operation. In the medium-to-large company, the instructions tend to be extensive technical (engineering) drawings and written procedures. In any company, particularly small manufacturers, the work instructions may take several forms as discussed below.

- Engineering drawings may be used if employees are trained to read and use them. Some of the how-to information comes from employee training rather than from drawings.
- Assembly drawings may contain parts list and quality acceptance criteria. A separate quality acceptance test and/or inspection procedure is not always...
necessary. An example of an engineering drawing for assembling a handle is exhibited at the end of this chapter. This drawing also includes some of the quality acceptance criteria for evaluating the handle in Notes 1 and 2. The parts list for the handle is on the page after the assembly drawing. Some manufacturers that manufacture simple devices use large sheets of paper for assembly drawings and include the parts list on it. The combination drawing results in instant availability of the parts list and reduces the number of drawings to be controlled. An example of an engineering drawing for assembling a cable and the associated parts list follows the handle assembly drawings.

- Exploded-view drawings are used when employees cannot read plan-view engineering drawings. Exploded-view drawings tend to be more "how to" than plan-view drawings. Exploded-view drawings are expensive to draft -- in some cases it may cost less to teach employees how to read and use ordinary plan-view drawings.

- Step-by-step written procedures may be used to detail how to perform specific tasks with check-off blanks to show that each specific task was performed. This type of procedure is commonly used for critical operations and where there is little or no visual indication of what has been done, such as for cleaning operations and for mixing chemicals.

Documentation may be supported by production aids such as labeled photographs, video tapes, slide shows, sample assemblies, or sample finished devices. All of these perform device master record functions and should be identified, and be current, correct, and approved for the intended operation.

The most commonly used aids are models or samples. There are two conditions that should be satisfied in order to use these aids. First, a written specification for the sample shall be contained in the device master record. This specification, of course, may be the same as the specification for the assembly or finished device to be manufactured. This specification shall be subject to a formal change-control procedure. Even though a model is available, the specification is needed for present and future product development, and for production control purposes. Second, the sample should:

- adequately reflect the device master record specification;

- be identified as an approved acceptable representative sample, which means it shall meet the company required workmanship standards; the sample need not be a working model if the nonworking condition is not misleading to employees being guided by the sample; and

- when appropriate, contain or be tagged with a drawing number, revision level, and control number (lot, serial, batch).

A card or tag as shown in the exhibits or an equivalent card may be used to identify and help control the use of samples of assemblies or finished devices. Such tags are usually covered by a clear plastic pouch and attached to the model or sample.

Samples and other aids such as photographs are subject to normal wear and tear in a production environment. Therefore, such aids should be adequately protected by a suitable means such as being located in a protected area, or covered by a protective pouch or container. Production aids should be periodically audited to make sure they continue to be suitable for the intended use. Section 820.100 contains requirements for corrective action. Corrective action may involve the use of samples, changes to the samples, or changes in the control of the samples.

Adequate Information
Although a manufacturer tries to document for the intended employees, there is a need to audit periodically to see how well the goal is being met. There are various means of determining if information in the device master record, production tools, and other production elements are adequate for a given operation and associated employees. These include analyzing the:

- assistance required by new employees;
- assistance required when a new device is introduced into production;
- confusion and hesitation;
- information exchanged among employees;
- "homemade" documentation drafted by the line employees;
- rework;
- products produced (productivity);
- complaints from departments that subsequently process the device; and
- customer complaints.

If any of these factors persist and are out of line with industry norms or with the previous production experience, then the manufacturer should take corrective action. Management shall review the quality system as directed by 820.20 and, thus, be aware of device quality problems or quality system problems such as listed above. The corrective action may include changes in supervision or documentation, adding new documentation, modifying the design, using different tools, modifying the environment, etc.

**Preparation and Signatures**

A separate device master record is required for each type or family of devices. Also, a separate device master record may be needed for accessories to devices when these are distributed separately for health care purposes. Such accessories are considered to be finished devices. In practice, if the device and accessories are made by the same manufacturer, the device master record for the accessory may be incorporated into the device master record for the primary device.

Within a family of devices, variations in the family may be handled by dash number extensions on drawing and procedure numbers. Usually, a top assembly or other major drawing contains a table/list of the devices in the family and lists the variable parameters for each member of the family.

Section 820.40 of the QS regulation requires that an individual(s) be designated to: review, date, and approve all documents required by the QS regulation including the device master record and authorize changes. An individual(s) with the necessary technical training and experience shall be designated to prepare and control device master records. In addition to requiring approval signatures on device master records, the QS regulation requires individual identification for a few other activities. For convenience, these activities along with the section numbers that require them are listed in Table 8.1.

**Table 8.1 GMP ACTIVITIES REQUIRING INDIVIDUAL IDENTIFICATION**

<table>
<thead>
<tr>
<th>Section</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>820.30(b)</td>
<td>Approval of Design Plans</td>
</tr>
<tr>
<td>820.30(c)</td>
<td>Approval of Design Input</td>
</tr>
</tbody>
</table>
### QSR Manual

<table>
<thead>
<tr>
<th>Section</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>820.30(d)</td>
<td>Approval of Design Output</td>
</tr>
<tr>
<td>820.30(e)</td>
<td>Results of Design Review</td>
</tr>
<tr>
<td>820.30(f)</td>
<td>Results of Design Verification</td>
</tr>
<tr>
<td>820.30(g)</td>
<td>Results of Design Validation</td>
</tr>
<tr>
<td>820.40</td>
<td>Approval of in Device Master Record or Changes</td>
</tr>
<tr>
<td>820.70(g)</td>
<td>Equipment Maintenance and Inspection Activities Performed</td>
</tr>
<tr>
<td>820.72(b)</td>
<td>Calibration Performed</td>
</tr>
<tr>
<td>820.75(a)</td>
<td>Approval of Process Validation</td>
</tr>
<tr>
<td>820.75(1)(2)</td>
<td>Performance of Validated Process</td>
</tr>
<tr>
<td>820.80(d)</td>
<td>Release of Finished Devices</td>
</tr>
<tr>
<td>820.80(e)</td>
<td>Acceptance of Activities Conducted</td>
</tr>
<tr>
<td>820.90(b)</td>
<td>Authorization to Use Non-Conforming Product</td>
</tr>
<tr>
<td>820.120(b)</td>
<td>Labeling Inspection</td>
</tr>
<tr>
<td>820.180(c)</td>
<td>Audit Certification</td>
</tr>
<tr>
<td>820.198(b)</td>
<td>Decisions Not to Investigate Complaints</td>
</tr>
</tbody>
</table>

The list is self-explanatory except for audit certification. When a manufacturer certifies in writing to FDA that quality system audits have been performed, the certification letter is signed by management having responsibility for the matters audited. Also note that the records in 820.70, 820.72, 820.80, 820.90(b), 820.120(b) and 820.160 are not part of the device master record but, instead, are part of the device history record (DHR). Records in 820.198(b) are part of the complaint files.

If a record that requires a signature is maintained on a computer, it is best if the designated individual(s) maintains an up-to-date signed printout of the record. Where it is impracticable to maintain current printouts, computer-compatible identifiers may be used in lieu of signatures as long as there are adequate controls to prevent improper use, proper employee identification, inaccurate data input, or other inappropriate activity. If identifiers such as coded badges and equipment keys are not controlled (i.e., not restricted to designated employees), then these will not meet applicable GMP "signature" requirements.

### Location of Records

Device master records shall be stored at the manufacturing establishment or at other locations (820.180) that are reasonably accessible to company employees responsible for the manufacturing activities and accessible to FDA investigators. Appropriate records may be maintained in computer data banks if the records are protected, change controlled, and readily accessible for use by responsible employees at all relevant facilities. It is acceptable for a manufacturer to maintain records on microfilm and discard the original hard copies. Microfiche and/or microfilm reductions may be used in lieu of original record retention if the following conditions are met.

- All reductions shall be readily available for review and copying by FDA investigators and designated company personnel at any reasonable time.
● All necessary equipment shall be provided for viewing and copying the records.
● Reproductions shall be true and accurate copies of the original record.

If the reproduction process results in a copy that does not reveal changes or additions to the original record, the original should be retained. In this situation, the reproduced copy and any image shown on a viewing screen should note any alteration from the original and indicate that the original record is available.

By maintaining the device master record, complaints and other records required by the QS regulation at the manufacturing establishment or other reasonably accessible location, responsible officials of a company can exercise control and accountability over the entire design, manufacturing, and postmarketing activities and, thereby, maximize the probability that the finished device conforms to its design specifications. This GMP requirement helps assure that responsible officials at the manufacturing establishment have ready access to those documents essential for producing devices and for conducting self-inspections, complaint investigations, failure analyses, audits, and corrective action.

The device master record is a single source document or file. Portions of this file may be kept in various locations. A device master record may exist as:

● one or more files or volumes of the actual records containing the information required by the QS regulation;
● a reference list of such documents and their location; or
● any combination of actual documents and/or reference lists.

These documents shall contain the latest DMR revisions, be signed, and be dated to show they have been checked for adequacy and approved for use (820.30, 820.40 and 820.181).

The QS regulation allows use of reference lists as a means to reduce the duplication of records, particularly duplication of general documents such as standard operating procedures (SOP's). General SOP's (not directly related to a product or process) however should be made a part of the quality system record (QSR) (820.186).

Use of a reference list also allows filing of device master record documents at several convenient locations. If the device master record contains a list of documentation, the actual documents shall be available for employee use and FDA inspection at the manufacturing site or other reasonably accessible locations. As noted above, this is a key and important GMP requirement. Typical locations of various device master records are shown in Table 8.2.

When performing an inspection of a company, FDA investigators shall have access to actual records for review and copying during reasonable business hours. FDA investigators review these records to determine if a manufacturer is complying with the QS regulation and with the Food, Drug, and Cosmetic Act.

Records deemed confidential by a manufacturer should be marked to aid FDA in determining whether or not specific information may be disclosed under the Freedom of Information Act. However, routinely stamping every document as "Confidential" defeats the purpose of requesting extra care be taken to protect a specific document or set of documents.
### Table 8.2 LOCATION OF DEVICE MASTER RECORDS

#### Typical Locations of Documents

<table>
<thead>
<tr>
<th>TYPE OF DMR ELEMENT</th>
<th>ORIGINALS</th>
<th>WORKING COPIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference list(s)</td>
<td>Engr. master file</td>
<td></td>
</tr>
<tr>
<td>Component drawings</td>
<td>Engr. or Manuf. Engr. master file</td>
<td>Manuf. or Procurement</td>
</tr>
<tr>
<td>Component acceptance procedures</td>
<td>SOP master file</td>
<td>Receiving department</td>
</tr>
<tr>
<td>Device Input specifications (final version)</td>
<td>Engr. master file</td>
<td>Marketing or Engineering</td>
</tr>
<tr>
<td>Manufacturing procedures</td>
<td>Engr. or Manuf. Engr. master file</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>Test specifications</td>
<td>Engr. master file</td>
<td>Engr. or Manuf. Engr.</td>
</tr>
<tr>
<td>Test procedures</td>
<td>Engr. or Manuf. Engr. master file</td>
<td>Manuf., QA, QC or Final Test</td>
</tr>
<tr>
<td>Inspection procedures</td>
<td>Manuf., QC, or SOP master file</td>
<td>Manufacturing or QC</td>
</tr>
<tr>
<td>Label drawings</td>
<td>Engr. master file</td>
<td>Engr., QA, or Manuf.</td>
</tr>
<tr>
<td>Label artwork</td>
<td>Artwork master file</td>
<td>Engr., Procurement</td>
</tr>
<tr>
<td>Label control procedures</td>
<td>Manuf., QC, or SOP master file</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>Specific cleaning procedures</td>
<td>SOP master file</td>
<td>Manufacturing</td>
</tr>
<tr>
<td>General cleaning procedures</td>
<td>QSR master file</td>
<td></td>
</tr>
<tr>
<td>System audit procedures</td>
<td>QSR master file</td>
<td></td>
</tr>
<tr>
<td>Employee training procedures</td>
<td>QSR master file</td>
<td></td>
</tr>
</tbody>
</table>

SOP = Standard Operating Procedure  
QSR = Quality System Record  
QA = Quality Assurance  
QC = Quality Control

#### Record Retention

The QS regulation in section 820.180(b) requires that all records pertaining to a device shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than two years from the date of release for commercial distribution by the manufacturer. Manufacturers of long-life products should make prudent decisions as to how long to keep records. For example, there may be no value in keeping records for long-life devices such as stretchers, surgical tools, containers, etc., forever if the probability is low that any post-distribution remedial activity will occur. For devices that require repair or capital equipment devices that probably will be updated, appropriate records
should be retained to support these repairs or modifications.

Device master record requirements apply to devices modified in the field by the manufacturer's representatives after the devices are commercially distributed. Modification of a device is manufacturing and the QS regulation covers all manufacturing of devices where the result is placed into commercial distribution. In any case, a manufacturer should be prepared to provide a rationale for its decision to discontinue record-keeping.

**DEVICE MASTER RECORD CONTENTS**

As discussed above, the device master record shows and/or tells employees how to perform specific functions related to the production of a device. The QS regulation does not dictate how this information is to be arranged or filed in the device master record and quality system record except that it shall be readily accessible. Because each device master record and quality system record contain many documents, an index of each is usually needed.

**Device Specification**

There may be many specifications in the device master record. One of these is the device specification. A device or product specification is a specific document in the device master record that briefly describes and gives all important details of the external characteristics of a device. The product specification may also contain some internal characteristics of the device that are important to the manufacturer and/or the users. The finished device specification is derived from the design input specifications in 820.30. For some devices, many of the external characteristics such as temperature tolerance are related to the environment in which the devices will function properly. For some in vitro products, the package insert is used by some manufacturers as the product specification for marketing purposes.

Generally a product specification will contain the device's:

- product trade and common name(s);
- intended use(s);
- performance characteristics and theory of operation;
- regulatory classification;
- physical characteristics;
- environmental limitations and product stability;
- important components and formula (if applicable); and
- user safety characteristics.

Table 8.3 contains a list of characteristics that often appear in product specifications; however, note that not all of the listed items will appear in the product specification for a given device.

In addition to defining and describing a device, a product specification is a communication tool which, if used in a timely manner, can help achieve some important results. First, it helps assure that everyone is talking about the same device and working toward the same objectives with respect to safety, effectiveness, human factors, configuration, labeling, packaging, processing, finished device acceptance, etc.

Ultimately, the device specification or a condensed version of it should be used in catalogs, or other product documentation, to aid communication between
salespersons and customers. If the marketing department uses the product specifications when preparing advertisements and catalog sheets, public relations with users will be enhanced because the marketing documents are based on proven scientific safety and performance claims for the actual device. The user has an opportunity to read the technical specifications of the item actually being offered for sale.

Thus the use of device product specifications will result in:

- improved communication between employees on a departmental and interdepartmental basis;
- less confusion and increased morale;
- an improved state-of-control;
- a higher probability of meeting cost, time, safety, effectiveness, and regulatory compliance objectives; and
- product literature that correctly describes the device for the prospective customer.

A sample product specification for a portable defibrillator is in the exhibits at the end of this chapter. This specification is long and detailed because it is a combined product and test specification, and because it is for a complex device.

**Specific Documents**

Specific documents are drawings, procedures, labels, data forms, etc., for a specific product or family of products. Product specific documents are almost always part of the device master record. The originals of specific documents are usually located in files in engineering or technical service departments. In most manufacturers, specific documents contain no general information; however, they often refer to general documents. (A list of specific and general documents is exhibited later in this chapter.) The number of specific documents for a given product line may range from about 10 to several hundred. If large numbers of documents are needed, an index is usually needed to help locate them, particularly for personnel that do not work in the drafting department or in technical services.

**Records for In Vitro Diagnostic Products**

The main differences between device master records for chemical-based in vitro products and for electromechanical products, such as instruments and artificial kidneys, is terminology and the relatively extensive use of written processing procedures and status reports for in vitro diagnostic products rather than a few assembly drawings and test/inspection reports. For example, device master records for chemical-based devices would contain a manufacturing section dealing with areas such as solution preparation and filling, whereas manufacturing sections for electromechanical products would cover operations such as assembly. Status records for weighing, mixing, filling, etc., are used for general control of in vitro products. Status reports are also used because it is often difficult to determine the status of in-process in vitro products by looking at them -- the opposite is usually true for most hardware devices. Records for in vitro devices also shall contain control data that allows components and kits to be traced [809.10(a)(9), etc.].

<table>
<thead>
<tr>
<th>Table 8.3 ITEMS THAT MAY APPEAR IN A DEVICE SPECIFICATION</th>
<th></th>
</tr>
</thead>
</table>

```
1. Name of Product

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Trade name</td>
<td>d. Chemical name</td>
</tr>
<tr>
<td>b. Trademark</td>
<td>e. Official name</td>
</tr>
<tr>
<td>c. Generic name</td>
<td>f. Common name</td>
</tr>
</tbody>
</table>

2. Performance Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Description/Intended use</td>
<td>e. Contraindications</td>
</tr>
<tr>
<td>b. Accessories</td>
<td>f. Input/Output requirements</td>
</tr>
<tr>
<td>c. Functional parameters</td>
<td>g. Human interface</td>
</tr>
<tr>
<td>d. Limitations</td>
<td>h. Other</td>
</tr>
</tbody>
</table>

3. Classification

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Regulatory</td>
<td>c. Functional</td>
</tr>
<tr>
<td>b. Commercial</td>
<td>d. Other</td>
</tr>
</tbody>
</table>

4. Physical Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Weight</td>
<td>e. Consistency</td>
</tr>
<tr>
<td>b. Size</td>
<td>f. Packaging</td>
</tr>
<tr>
<td>c. Color</td>
<td>g. Power requirements</td>
</tr>
<tr>
<td>d. Form/Shape</td>
<td>h. Other</td>
</tr>
</tbody>
</table>

5. Environmental Limitations

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Operating temperature range</td>
<td>f. Moisture protection</td>
</tr>
<tr>
<td>b. Storage temperature range</td>
<td>g. Pressure, altitude limits</td>
</tr>
<tr>
<td>c. Vibration and shock range</td>
<td>h. Electromagnetic interference</td>
</tr>
<tr>
<td>d. Voltage range</td>
<td>i. Electrical transients</td>
</tr>
<tr>
<td>e. Humidity range</td>
<td>j. Shelf life/Other</td>
</tr>
</tbody>
</table>

6. Important Components

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Active ingredients</td>
<td>f. Service labeling</td>
</tr>
<tr>
<td>b. Major subsystems</td>
<td>g. Components/items supplied by user</td>
</tr>
<tr>
<td>c. Diagnostic kit materials</td>
<td>h. Software</td>
</tr>
<tr>
<td>d. Accessories</td>
<td>i. Periodic Warranty/Other</td>
</tr>
<tr>
<td>e. Labeling</td>
<td></td>
</tr>
</tbody>
</table>
7. User Safety and Performance Considerations

a. Chemical                                       e. Personnel training
b. Electrical                                        f. Periodic testing
c. Thermal                                          g. Maintenance
d. Mechanical sharp, moving parts      h. Other

QUALITY SYSTEM RECORD DOCUMENTS

Quality system record (QSR) (820.186) or general documents are used for many activities that are essential to operating a manufacturing establishment --
these are not specific to any given product even if the company produces only one product. Thus, the quality system record includes general documents such
as standard operating procedures (SOP's) and standard quality assurance procedures (QAP's). If the company added another product line, the basic content of
these documents would undergo none or only minor changes.

In a typical manufacturing operation, general QSR, SOP, and QAP documents may include the following:

| Employee training procedures | Supplier assessment policy |
| Cleaning procedures          | General design control procedures |
| Insecticide use-removal procedures | Component inspection procedures |
| Air conditioning/heating procedures | Workmanship standards |
| Tool kit policy             | Design review policy/procedure |
| Safety procedures           | Label review policy/procedure |
| Procurement procedures      | Sterile water system maintenance |
| Returned goods policies     | Calibration policy |
| Drawing numbering system    | Complaint handling procedure |
| Change control procedure    | Recall procedure |
| Service policy              | Deviation review policy/procedure |

The above list is not all inclusive. Medium-to-large companies tend to have many of these general documents to guide management in maintaining consistent
operations. A very small company may have only the most essential and appropriate of these documents such as procedures for design controls, drawing
numbering system, change control, employee training, use of hazardous materials, etc.

The original copy of each general procedure is filed in the department specified by management as having responsibility for maintaining that procedure, or it
is filed in an automated system with access by the designated departments. The working copies of the above procedures are usually located in SOP manuals
and QA manuals. The procedures are usually numbered and arranged in a logical order by topic. The QS regulation does not require manufacturers to keep
quality system record documents in SOP or QA manuals; however, the experience of many industries has demonstrated that such manuals are worthwhile if they are kept current and contain only the real working procedures.

WRITTEN PROCEDURES

Many sections of the QS regulation require written procedures for instructions in performing various quality system, design product acceptance, QA, and manufacturing tasks. Certain devices such as in vitro products, because of the nature of the manufacturing operations, tend to have a relatively large number of written procedures.

Written procedures are used for quality system audits, product development, manufacturing, post-marketing activities, etc., to:

- improve communication and guidance;
- assure consistent and complete performance of assigned tasks; and
- promote management of operations.

In large manufacturing facilities involving many operations and people of various skill levels, many written procedures are usually necessary. In a small manufacturer, communication lines are usually short, few people are involved, and management is readily available to provide guidance, so that the need for written procedures is usually less than for a larger manufacturer.

A manufacturer, particularly a small manufacturer, may conclude that GMP requirements for written procedures are not applicable for a particular operation. Although the number of written procedures may vary, all manufacturers are required to maintain a device master record (820.181) for each type or family of devices they produce.

Often training and work experience alone or combined with drawings, photographs, and models are valid substitutes for written procedures. For example, machinists are typically skilled personnel who fabricate components and finished devices using dimensional drawings for guidance instead of written procedures. The company and FDA investigator will evaluate each situation based on the training and knowledge of the operators and the control needed to meet device specifications. Typically, a written procedure is not necessary when:

- the activity is very simple;
- the activity is relatively simple and models are used as production aids;
- straightforward quantitative rather than qualitative standards determine acceptability; and
- the operation is performed by personnel highly skilled relative to the task being performed.

Written procedures and associated history or status records, however, are often needed for activities where there is no change, such as color, texture, or form, to indicate that the activity has been performed correctly.
Developing Procedures

Developing written procedures is relatively labor intensive and time consuming, which may lead to use of "back-of-the-envelope" notes instead of formal procedures. Likewise, changing these procedures is time consuming, which may lead to delays or forgetting to make the changes. Drafting or changing written procedures is also prone to errors. Therefore, manufacturers are encouraged to use computers and low-cost printers as word processors to aid in writing and changing procedures. With the use of computers, these tasks become easier thereby increasing the probability that they will be performed correctly and when needed. Computers can also be used for generating and maintaining device master record indices and complaint files, and performing a host of other GMP related activities.

There is a method for developing procedures that will result in short, clear procedures that help solve real problems. The first two steps are:

- identify the problems to be solved; and
- decide if new or modified procedures are needed to help solve or reduce the problems.

Events that point to a problem are excessive rework, employee confusion, customer complaints, recalls, etc. These "pointers," however, may not be the real problem. The real problem may be inadequate design, components, equipment, maintenance, operational techniques, documentation, environment, etc. The real problem should be identified before it can be solved. A written procedure may or may not be needed to help solve the problem.

The real problem can be identified by careful analysis of:

- the "pointers" noted above,
- device design,
- process design,
- process flow and employee work habits (operational analysis),
- test and inspection data, and
- any other activity related to the quality of the device.

Operational analysis is aided by flow-charting which is a step-by-step chart of the minute details of the operation. Thus, a flow chart is much more detailed than a QA audit report and is very helpful in determining what is actually happening in a particular manufacturing operation. This knowledge may lead to a solution of manufacturing and quality problems. An example of a flow chart appears in the exhibit section of chapter 10.

From a company quality system, interface, and personnel management viewpoint, the problem, the reason for flow-charting the given activity, etc., should be discussed with affected personnel. Their input should be requested with respect to identifying and solving the real problem.
presented by the flowchart and the experience gained while producing the chart, the QA auditor is better able to:

- analyze the particular operation with respect to process requirements;
- determine what needs to be added, modified, or deleted to solve any problems or improve performance; and
- if needed, write or modify a procedure to cover the new way of performing the activity.

Content of Procedures

Written procedures are widely used and industry experience has shown that these should contain the following items:

- company identification and a procedure title;
- an identification or control number with a revision level code;
- an approval signature, and date the procedure becomes effective;
- the number of pages (e.g., sheet 1 of 4) in the procedure or another means to indicate that the employee has the complete document; and
- step-by-step instructions for performing the required activities

The effective date may be the same as the approval date. Also, the effective date may appear on a separate document such as an engineering change order (ECO) form. The main body of the procedure should cover, as appropriate:

- subject, scope, and objectives;
- who is assigned to perform the task;
- what activity or task is to be performed;
- when and where the task is to be performed; and,
- how to perform the task including what tools, materials, etc., to use.

Particularly for the new employee, it is important for the procedure to state the reason for performing a function and the reason it is to be performed in a certain way. Background information such as this helps the employee to understand an assignment and remember how to perform it. For example, when working on static sensitive integrated circuits that are easily damaged by electrostatic potentials, unskilled employees need to understand why they have to be grounded, work on grounded mats and, especially, why they are not allowed to wear certain fabrics while at work. Likewise, employees working in environmentally controlled, clean manufacturing areas need to be told about invisible microbes and particulates, and that humans are the major source of these unwelcome contaminates. If so informed, employees are more likely to follow the operational procedures for working in controlled areas.

The task description in each procedure should cover appropriate details such as:

- the expected and actual results from performing the tasks, such as what data to collect and how to analyze, file, and report it;
- what to do with the component, in-process device, or finished device if such is involved; and
● any related activities that need to be performed in order for the overall operation to remain in a state-of-control or for the device to meet the company
device master record specifications.

If the procedure being developed, for example, covers change control, the procedure should also cover related activities such as changes to labeling. Consider
a change to a device where an analog meter is replaced with a digital meter -- obviously the instruction manual (labeling) and service manual also need to be
modified. Otherwise the finished device:

● may not meet company labeling policies;

● is misbranded because it does not meet the labeling requirements of the FD&C Act; and,

● is adulterated because the change does not meet the change control requirements of the QS regulation.

After the procedure is drafted, if appropriate, it should be reviewed with the affected personnel before it is approved and implemented. During the initial
implementation, the use of the procedure should be monitored. Then, based on actual experience in using the procedure, if necessary, it should be modified to
more exactly meet the need of the operation or process.

CHANGE CONTROL

The QS regulation in section 820.181 by reference to 820.40 requires that any changes to the
device master record be authorized by the signature of a designated individual(s). Change control requirements also appear throughout the QS regulation. The
control of changes to devices, processes, and the associated device master records is one of the most important elements of a quality assurance system. The
requirements for a successful change control system are so extensive that the entire next chapter of this manual is devoted to changes and associated
procedures.

EXHIBITS

Reprinted on the next pages are typical documents (records) that appear in device master records. Manufacturers may use these as guides in developing their
device master records.

Documents That May Appear in a Device Master Record

The first exhibit is a list of documents that might appear in device master records. Each device master record would contain only those documents that are
applicable for a specific device. Some of the listed documents are general rather than product specific. General documents are usually called standard
operating procedures (SOP's) and, if necessary, are referenced in the device master record rather than actually being included. The general documents are
usually part of the quality system record (QSR).
Device Master Record Index

This exhibit is a policy/procedure for drafting a device master record index. An index is also known as a document plan, table of contents, etc. An example of a device master record index follows immediately after the policy/procedure. Note that this particular policy/procedure contains definitions. It is important that procedures contain definitions, in a case like a complex device master record index where employees may not be familiar with the terminology.

Product Specification for a Portable Defibrillator

Finished device or product specifications are the backbone of any device master record. The one illustrated as the third exhibit is for a complicated piece of equipment and is, therefore, extensive. For long documents it is recommended that a table of contents be incorporated as was done in this specification. Appendix A and B of this specification are not exhibited.

Zener Diode Specification

This specification for a non-complicated part contains the necessary information to describe the item in sufficient detail for the correct part to be procured per the 820.50 Purchasing Controls.

Label Example

A sample label is exhibited. Labels and labeling are components and their specifications, art work, etc., are part of the device master record. As for any component, labeling shall be specified (documented). The resulting device master record document shall be reviewed, approved, change controlled, and stored such that it may be readily accessed. Such records are used to meet requirements such as those in 820.50, 820.80(b), 820.80(d), 820.120(b), 820.120(e), etc.

Handle Assembly and Parts List

This exhibit is an engineering drawing and parts list for a handle assembly. Engineering drawings, parts lists, or formulations are a vital part of many device master records. In this case, the engineering drawing not only details how this assembly is to be made, but there is also important information in the notes on the drawing. If properly trained and with sufficient experience, employees are able to use this drawing as the instructions for assembly of this handle. A written assembly procedure is not necessary.

Cable Assembly and Parts List

This exhibit is similar to the handle assembly mentioned above. The type of drawing used and information on a drawing can aid a manufacturer in reducing paperwork needed to manufacture a specific product.

Device Master Record Index for Amylase

This document is a device master record index for an in-vitro diagnostic product. Proprietary information in this index is replaced by X's. The company that
prepared this index uses purchase specifications and raw material specifications. Some manufacturers, particularly small companies, specify and purchase standard, routine items such as bottles and caps by using catalog numbers. Component specification drawings are not always used for routine items such as standard bottles.

Product Description

This exhibit is a product description for an in vitro diagnostic product. The standard operating procedures, quality control procedures, manufacturing flow sheets, and notes mentioned in this product description are not reprinted herein.

Amylase Diluent Solution

This exhibit is the procedure for making a batch of amylase solution. In this procedure, note that for each step the company requires the initials or signature of the person actually performing the operation and of the individual who checked that person's performance of the operation.

Filling Record - Liquid, Non Freeze Dried

This is an exhibit of a filling record used for liquid products to document the steps in a filling operation. The completed filling record becomes a part of the device history record (DHR) for the batch being filled.

Finished Product Release Form

This form is used to record that the device history record is complete for a lot of product, the product meets specifications, and the lot may be approved for release.

Production Sample Card

This exhibit shows both sides of a card or tag used to identify and help control the use of manufacturing aids such as samples of assemblies or finished devices. The use of a sample identification card is described in the main text of this chapter.

Shop Order Traveler

The last exhibit is two job travelers or job followers. These cards, forms, tags, etc., are used to identify a batch or sub-batch of in-process assemblies as they are passed from one department to another. Where needed, travelers are used to reduce mixups and confusion and, in general increase the state-of-control of an overall manufacturing operation. Travelers help meet the general requirements of 820.60, Identification, and the specific requirements of 820.86, Acceptance Status.

DOCUMENTS THAT MAY APPEAR IN A DEVICE MASTER RECORD

1.0 Device Master Record Index
The device master record Index is a table of contents which is used for convenience. It may be known as a:

Device Master Record Index
Documentation or Device Master Record Unit;
Documentation Plan;
Product Tree;
Documentation Index;
Product Structure; or

Bill of Materials (if it also lists the device master record documents).

2.0 Device Specifications

(Device specifications are described in the chapter text.)

3.0 Manufacturing Information

3.1 Index

(Optional. See 1.0 above for total table of contents.)

3.2 Formulation or top assembly drawing

3.3 List of components

1. List of ingredients (including grade or type)

2. Bill of materials (i.e., component list usually arranged by subassembly or other sub-product level or by process steps)

3. Formula

3.4 Procurement documentation
1. Specifications

2. Drawings

3. Certificate of compliance requirements

4. Supplier Assessment procedures

3.5 Device documentation

1. Fabrication drawings

2. Surface finish procedures

3. Subassembly drawings

4. Wiring and piping diagrams

5. Assembly procedures

6. Assembly drawings

7. Reference documentation

a. Wiring and piping schematics

b. Test specifications

8. Sub-batch procedures

9. Blending or mixing procedures

10. Solution procedures

11. Final formulation procedures

12. Software packages
3.6 Precautions and special notations

1. Apparel
2. Cleaning
3. Storage conditions
4. Filling, mixing conditions
5. Hazards and safety precautions

3.7 Equipment, lines, and procedures

1. Process lines
2. Assembly lines
3. Vessels
4. Mixers, tools
5. Molds
6. Machine maintenance procedures
7. Calibration procedures
8. Setup procedures
9. Operating procedures
10. Process flow charts

3.8 Sterilization procedures

1. Procedures for ethylene oxide, radiation, filtration, steam, etc.
2. Handling and flow procedures

3. Cycle parameter specifications

4. Diagrams for loading products in the chamber

3.9 Production control documentation

1. Inspection procedures

2. Test procedures

3. Blank job travelers

4. Blank inspection/test forms

5. Instrument charts

6. Reporting forms

7. Approved deviations

4.0 Labeling and Packaging

4.1 Index (Optional. see 1.0 above.)

4.2 Labeling

1. Label drawings

2. Labeling drawings

3. Label/labeling review procedures and forms

4. Production control procedures and history record forms

5. Instruction manuals
6. Service manuals

7. Customer software

8. Customer feedback forms

4.3 Packaging

1. Package drawings (usually includes labeling information)

2. Closure drawings

3. Filling and/or packaging procedures

4. Packing procedures

5. Special shipment procedures

4.4 Storage requirements

1. Temperature

2. Humidity

3. Shelf-life

5.0 Control Procedures and Activities

5.1 Index (optional. see 1.0 above.)

5.2 Inspection procedures

1. Incoming

2. In-process

3. Finished devices
4. Process control charts

5. Blank data reporting forms

5.3 Test procedures

1. Incoming

2. In-process

3. Pretest conditioning

4. Finished device

5. Process control charts

6. Blank device history record forms

7. Automated test programs and/or software

6.0 Final Release

6.1 Release document review list

6.2 Distribution procedures

6.3 Blank device history record forms

Title: DEVICE MASTER RECORD INDEX

Policy No. ______________  Rev. ______________  Date ______________

Approval ____________

1.0 Purpose and Scope: To prescribe the responsibilities for preparing device master record (DMR) Indices and content of DMR Indices (lists).

2.0 Policy: A DMR Index shall be prepared and maintained for all devices being developed or manufactured.
3.0 Definition: A DMR Index is a table of contents for the device master record of a device. It also contains information on the breakdown of the device into assemblies and/or manufacturing steps. It is called a document plan during planning and early development of a new product. A DMR is:

3.1 An aid in proposing, planning, tasking, and reviewing projects;

3.2 A framework for preparing drawings, parts lists, and test equipment lists;

3.3 A means of familiarizing personnel with the device configuration;

3.4 A current record and status of the physical configuration of the device and a list of all reference documentation required; and

3.5 An index to the product-specific documentation required for procurement of components, manufacture, and evaluation of a device.

4.0 Procedure:

4.1 Preliminary document plans may be generated for the convenience of Engineering. Upon completion of the design when formal records are needed, a formal document plan will be initiated.

4.2 The configuration and structure of the document plan is set by the Engineering, Manufacturing Engineering, and Drafting Supervisors.

4.3 After agreements, the plan will be drawn, document numbers assigned, status of drawings indicated, and the plan approved by Engineering and Manufacturing. All non-product specific documents such as standard operating procedures that are used during production of the device will be listed on the plan. (Because the plan is now complete, it is a DMR Index.)

5.0 Example: Part of an index in "tree" form is on the following pages. A "tree" form allows a large amount of information to be displayed in a small area. Each column covers a major section of the documentation such as the battery charger. The index contains codes to convey additional information such as a rectangle with a dark triangle in a top corner or a mark such as "#" to indicate a parts list is included with a particular drawing.
(Sample for training purposes only. Do not use for technical parameters.)

PRODUCT SPECIFICATION PORTABLE DEFIBRILLATORS

CONTENTS

PRODUCT SPECIFICATION

1.0 Reference Documents

2.0 Overall Description

3.0 Configurations

4.0 Functional Characteristics

5.0 Performance Characteristics

APPENDIX A (not reprinted in this manual)

TEST RECOMMENDATIONS
APPENDIX B (not reprinted in this manual)

TEST POINT AND BOARD INTERCONNECT SIGNAL

DEFINITIONS

Throughout this Product Specification * indicates need for test.

NOTE: Values not in parentheses refer to Models D320 and D320W. Values in parentheses refer to Models D400 and D400W.

<table>
<thead>
<tr>
<th>LTR</th>
<th>DESCRIPTION</th>
<th>DATE</th>
<th>APPROVED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pilot released per ER - 3556</td>
<td>04/23/75</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Revised and Retyped per ECO - 3968</td>
<td>01/27/76</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Revised and Retyped per ECO - 4225</td>
<td>05/28/76</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Revised per ECO - 4636</td>
<td>12/28/76</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Released to Production per ERN - 4645</td>
<td>03/10/77</td>
<td></td>
</tr>
</tbody>
</table>

Title: PRODUCT SPECIFICATION PORTABLE DEFIBRILLATORS

DR BY: A J Lucas         DATE: 4/15/75         DWG NO. 04300538         Sheet 1 of 14

APP'D:                     Date: 3/10/77

PRODUCT SPECIFICATION PORTABLE DEFIBRILLATORS

D320, D320W, D400, & D400W

1.0 REFERENCE DOCUMENTS

1.1 Portable Defibrillators D320/400 and D320W/400W 23990081-XX
1.2 Adult Anterior Paddles 24990082-01 450 AA
1.3 Adult Anterior-Posterior Paddles 24990113-01 450 APA
1.4 Adult Anterior Paddles 24990114-03 450 AI
1.5 Pediatric Anterior Paddles 24990082-02 450 PA
1.6 Pediatric Internal Paddles 24990114-02 450 PI
1.7 Infant Internal Paddles 24990114-01 450 II
1.8 Adult Anterior Paddles with Remote Charge 24990082-03 450 AAR
1.9 Patient Cable Assay. 3 Electrode -21 D24990118-01
1.10 Tube XXXXXX (712) 1042507001
1.11 D320/400 Shipping List
1.12 D320/400 Operators Manual
1.13 D320/400 Maintenance Manual

2.0 OVERALL DESCRIPTION

The D320/400 (Ref. 1.1) is a portable defibrillator with integral isolated input, solid trace, ECG monitor scope. The D320/400W contains in addition a 40 mm strip chart recorder. They may be used for non-synchronous ventricular defibrillation or synchronous conversion of arrhythmias. Power is derived from internal rechargeable batteries or from the AC power line whenever the unit is connected to the AC power line via the internal charger.

Standard accessories included in the D320 Shipping List (Ref. 1.11) are:

1 - Adult Anterior Paddle Set (Ref. 1.2)
1 - Patient Cable-21(Ref. 1.8)
1 - Tube XXXXXX Electrode Paste (Ref. 1.9)
Optional Accessories are alternate paddles described in section 4.

1. CONFIGURATIONS

23990081-01 Battery Operated Defibrillator - D320 (120V)

23990081-02 Battery Operated Defibrillator - D320 (220V)

23990081-03 Battery Operated Defibrillator with Writer - D320W (120V)

23990081-04 Battery Operated Defibrillator with Writer - D320W (220V)

2399 Battery Operated Defibrillator - D400 (120V)

2399 Battery Operated Defibrillator - D400 (220V)

2399 Battery Operated Defibrillator with Writer - D400 (120V)

2399 Battery Operated Defibrillator with Writer - D400W (220V)

4.0 FUNCTIONAL CHARACTERISTICS

4.1 DEFIBRILLATOR FUNCTIONAL CHARACTERISTICS

The defibrillator becomes operational in the non-synchronous mode when the power switch is turned ON and the paddle connector is attached. A charge cycle is initiated by depressing and holding the MANUAL CHARGE button until the desired charge is reached. Automatic charge to 160 (200) or 320 (400) joules is accomplished by depressing the AUTO CHARGE 160 (200) or AUTO CHARGE 320 (400) buttons respectively. An audible tone and a DELIVERED ENERGY bar display on the scope indicate when a charge is in process. When the charge cycle is complete, the audible tone stops and the DELIVERED ENERGY meter indicates the amount of energy to be delivered. The stored energy is delivered in the form of an Edmark waveform by pressing the buttons located on the anterior paddles or, if interior paddles are used, pressing the INTERNAL PADDLE switch located on the control panel.

For safety and equipment protection, a charge cycle is followed by an automatic time out that dumps the stored energy (disarms) after 45 seconds if energy is not delivered or the charge button pressed again within the time out period. The stored energy is also automatically dumped when the power switch is turned OFF. The operator may disarm the unit by depressing the DISARM button.
4.1.1 Delivered Energy Indicator

The DELIVERED ENERGY INDICATOR displays the energy to be delivered into a 50 ohm load as a horizontal line at the top of the CRT screen. When a charge is initiated, the end of a solid bar will follow the amount of energy to be delivered.

4.1.2 Paddle and Accessory Storage

A molded paddle holder is in the defibrillator front panel cover for one set of anterior-anterior adult defibrillator paddles. One (D320W/400W) or two (D320/400) accessory holders are located below the front panel to hold cables, electrodes, and paste. Under normal usage, the defibrillator is stored or transported with defibrillator cables connected. This approach minimizes the number of steps needed to bring the defibrillator from an idle state to the emergency non-synchronous mode.

4.1.3 Anterior-Anterior paddles

Anterior-anterior paddle assemblies are available with two electrode sizes: adult 8.5 cm (Ref. 1.2) and pediatric 5.0 cm (Ref. 1.7). Each assembly consists of a connector, two paddles with discharge buttons, and a dual coiled cord extendable to 10 feet.

Ethylene oxide sterilization is the only permissible sterilization technique for all of these paddles.

4.1.4 Anterior-Anterior Paddles with Remote Charge (Optional)

Same as 4.1.3 except one paddle will have a charge button that functions identically to MANUAL CHARGE button on the front panel (Ref. 1.8).

4.1.5 Anterior-Posterior Paddles

An anterior-posterior paddle assembly (Ref. 1.4) is available for use only on adults. It consists of an anterior paddle identical to the 8.5 cm paddle in a 4.1.3, a posterior 12 cm paddle, a dual 10ft. coiled cord, and connector.

4.1.6 Internal Paddles

Internal paddle assemblies are available with three electrode sizes: adult 8.5 cm (Ref. 1.4), pediatric 5.0 cm (Ref. 1.5), and infant 2.5 cm (Ref. 1.6). Each assembly consists of a connector, 2 paddles, and a dual coiled cord extendable to 10 ft.

4.2 ECG AMPLIFIER AND SOLID TRACE SCOPE FUNCTIONAL CHARACTERISTICS

4.2.1 ECG Amplifier

The ECG amplifier is an isolated, variable gain amplifier which feeds the display, QRS detector, and output jack. Input to the amplifier is through the defibrillator paddle connector or through the patient cable. A lead selector switch selects the paddles, or leads I, II, or III for input. The amplifier incorporates
the following features:

1. Slew Rate Limit - Limits the slew rate and, therefore, the amplitude of the pacer pulses so that they can be seen on the display and will not trigger the QRS detector in most lead configurations.

2. Fast Recovery Circuit - Returns the signal to on screen limits within 0.5 seconds after defibrillation or other overload.

4.2.2 Solid Trace Display

The solid trace display shows the last 4 seconds of ECG waveform on the screen. The waveform appears as if a strip chart recorder were writing the ECG at the right hand edge of the screen and the paper was being pulled from right to left. Current information is displayed at the right of the screen with information becoming increasingly older towards the left. When operating the defibrillator in the synchronous mode, sync pulses appear showing where the energy would have been delivered had the discharge buttons been pushed. The waveform may be stopped or "frozen" for review by pushing the latching FREEZE button.

4.3 HEART RATE METER FUNCTIONAL CHARACTERISTICS

The heart rate meter displays heart rate as a bar at the screen bottom. The heart rate is also compared to alarm limits that are displayed on the same bar. When a limit is exceeded for longer than three seconds, the red alarm led blinks, an audible alarm sounds, and the hard copy writer runs (D320W/400W only). Alarms are disabled or reset by putting the LOW LIMIT knob fully counter-clockwise and the HIGH LIMIT fully clockwise. In this position the limit indications are not displayed on the screen.

The threshold for QRS detection is automatically adjusted depending on the amplitude of the QRS complex. The minimum threshold is equivalent to 0.6 cm on the scope display. At maximum gain, a 0.3 mv QRS complex will be detected. Detection of a complex will cause an audible beep if the BEEP push-button is depressed. Proper adjustment of the gain control will result in an R-wave amplitude on the screen of one to two cm.

*4.4 SYNCHRONIZED CARDIOVERTER FUNCTIONAL CHARACTERISTICS

The synchronizer detects the peak of the R wave and, after the discharge buttons on both defibrillator paddles have been pushed, delivers the stored energy. The QRS amplitude must be set to at least 0.6 cm on the scope display using the SIZE control. QRS detection is verified by an audible QRS beep and by a SYNC pulse displayed on the scope at the time relative to each QRS complex that the energy would have been delivered.

4.5 WRITER FUNCTIONAL CHARACTERISTICS (D320W/400W only)

The D320/400W is equipped with a 40 mm direct hard copy writer. The writer is started manually by the RECORD push-button on the front panel or automatically on alarm. No other controls are provided. Gain of the writer is equal to the gain of the scope. Therefore, setting the QRS size control to a convenient point for the scope will produce a reasonable gain for the writer. Centering of the writer is automatic to within approximately .25 cm. An internal stylus heat adjustment is provided. An external control is not needed due to the regulation of the stylus power supply.

4.6 MODES OF OPERATION
The defibrillator has two modes of operation: non-synchronous defibrillation and synchronous defibrillation. The defibrillator is always in the non-synchronous defibrillation mode when power is turned on. It can be switched from the non-synchronous mode to the synchronous mode by pressing the SYNC ON push-button. It can be returned to the non-synchronous mode by pressing the SYNC OFF push-button. Synchronous mode is indicated by a SYNC light on the front panel and by sync pulses appearing on the scope coincident with QRS detection.

*4.7 OPERATOR CONTROLS

4.7.1 ON/OFF

A two push-button switch turns on the ECG amplifier and Solid TraceScope and puts the unit in the non-synchronous mode when ON is depressed.

When OFF is depressed it dumps (disarms) the defibrillator capacitor and switches off all power to the unit. Closing the front cover automatically depresses OFF.

4.7.2 MANUAL CHARGE

A momentary push-button that causes the capacitor to be charged while depressed.

4.7.3 AUTO CHARGE 160 (AUTO CHARGE 200)

A momentary push-button which initiates an automatic charge to 160 joules delivered.

4.7.4 AUTO CHARGE 320 (AUTO CHARGE 400)

A momentary push-button which initiates an automatic charge to 320 joules delivered.

4.7.5 PADDLE CHARGE (Optional)

A momentary push-button located on the right paddle which functions identically to the MANUAL CHARGE push-button.

4.7.6 SYNC ON/SYNC OFF (Labeled SYNC/DEFIB ON D400/400W)

Two momentary push-buttons used to select synchronous or non-synchronous mode of operation. Pressing SYNC ON after the power is turned on puts the unit in the synchronous mode and illuminates the SYNC light. The unit is put in the non-synchronous mode when power is turned on or by pressing SYNC OFF when operating in the synchronous mode.

4.7.7 DISARM
A momentary push-button that is used to dump the internal stored charge. It is used if a lower energy than the one already selected is desired, or if no more countershocks are to be delivered.

4.7.8 QRS SIZE

A potentiometer used for setting the gain of the ECG amplifier. Gain may be varied from X300 at fully CCW to X3000 at fully CW. At center position, the gain is X1000.

4.7.9 FREEZE

A latching push-button that causes the scope to cease updating.

4.7.10 1MV

A momentary push-button that injects a 1 mv +/- 2.5% signal.

4.7.11 BEEP

A latching push-button that activates the QRS beep when depressed.

4.7.12 HIGH LIMIT

A potentiometer used for setting the alarm high rate limit over a range of at least 100 to 250 BPM. It is set to 120 BPM with knob pointer is straight up.

4.7.13 LOW LIMIT

A potentiometer used for setting the alarm low rate limit over a range of at least 0 to 150 BPM. It is set to 60 BPM with knob pointer is straight up.

4.7.14 RECORD

A latching push-button that starts the writer when depressed. The writer is always started on alarm.

4.7.15 LEAD SELECT

Four interlocking push-buttons labeled PADDLES, I, II, III that select paddles or standard leads I, II, III respectively as input to the ECG amplifier. A three-lead cable with RA, LA, and LL (which may be labeled R) can be used.

*4.8 INDICATORS
4.8.1 BATTERY LOW

A red lamp that begins flashing when the battery has a minimum of ½ hour of continuous monitoring capacity left or 2 charges to 320 joules (1 charge to 400 joules). The lamp flashes to indicate circuit operation when power is turned on.

4.8.2 SYNC

An amber LED that illuminates when the unit is operating in the synchronous mode.

4.8.3 DELIVERED ENERGY, JOULES

An illuminated bar that indicates the energy in joules to be delivered into a 50 ohm load.

4.8.4 TEST

A light located on the defibrillator paddle holder that illuminates when a counter shock of at least 300 joules is discharged into the paddle holders.

4.8.5 ALARM

A red light that flashes during an alarm.

4.8.6 LINE

Two red lights that illuminate when AC power is being received by the unit.

4.8.7 QRS Beep

An audible tone that is produced every time a QRS complex is detected when the BEEP push-button is depressed.

4.8.8 Charging

A audible tone that increases in pitch as the capacitor charges.

4.8.9 Sync Pulse

A negative pulse displayed on the ECG trace with its center within 20 ms of where the energy should have been delivered if the DISCHARGE BUTTON(S) had been pushed.
4.8.10 Heart Rate Bar

An illuminated bar graph showing Heart Rate and alarm limit settings.

*4.9 CONNECTORS

4.9.1 Defibrillator Paddle Connector

G pin High Voltage Connector

Pin D - High Voltage Paddle Lead

Pin A + High Voltage Paddle Lead

Pin F Ground

Pin C INT PDL - (Internal Paddle Jumper)

Pin B FDLSW - (Paddle Switch)

Pin E RMT CHG - (Remote Charge Switch)

4.9.2 Isolated Input Connector

5 pins MS series Connector - Located on front panel.

Pin A Right Arm

Pin B Left Arm

Pin C Left Leg

Pin D Left Leg

Pin E Left Leg

4.9.3 ECG/Output Connector
3-wire phone jack on front panel

Tip - ECG Output

Ring - Signal Ground

Sleeve - Chassis Ground

5.0 PERFORMANCE CHARACTERISTICS

5.1 DEFIBRILLATOR OUTPUT

5.1.1 Waveform: Monophasic pulse (Edmark Waveform)

5.1.2 Energy Range: 10-320 joules delivered into a 50 ohm load.

D320/320W

5.1.3 Energy Accuracy: DELIVERED ENERGY INDICATOR OR AUTO 320 (400) and AUTO 160 (200) push-buttons

Error less than 10% or 4 joules, whichever is greater, into 50 ohms and 25% or 4 joules, whichever is greater, into a 25 to 100 ohm load when measured in accordance with XXX recommendations.

5.1.4 Pulse Width: 95% of the energy delivered in <5 ms into 50 ohm load.

5.1.5 Charge Time:

D320/320W

Charges to 320 joules in 10 sec. max. 8.5 sec. typical.

Charge Time:

D400/400W

Charge to 400 joules in 12 sec. max. 10.5 sec. typical.

5.1.6 Pulse Rate:

<5

Deliver 15 400-joule counter shocks in minutes.

5.1.7 Energy Loss Rate:

<15% in 30 seconds.

5.1.8 Charge Dump Time

<25 volts left in 4 seconds and <2 joules in 3 minutes after activation of capacitor dump circuit.

5.1.9 Isolation

Withstands 8 KV DC from either paddle to chassis with relay in fire position.
**ECG AMPLIFIER**

*Frequency Response:* .5 to 40 Hz. +0, -3 db max. from isolated input connector to ECG output on front connector or scope display at 1 cm scope deflection.

*Risk Current:*
- < 10 ua at 120 v 60 Hz without patient cable.
- < 20 ua with 120 VAC applied to electrode end of ECG patient cable.

*Gain:* adjustable x300 to x3000. x1000 at nominal gain position.

Input Impedance: > 1 megohm differential, DC to 60 Hz through patient cable.

Input Offset Tolerance: > 1 volt

Input Dynamic Range: +/- 3.5 mv at nominal gain setting.

*Isolation Voltage:* 2500 volts RMS at 60 Hz from any patient lead or combination of patient leads to AC line for one minute.

Defibrillator Protection:
- Will withstand 5 pulses at 20 second intervals from defibrillator set to 400 ws delivered energy and delivered across a 100 ohm load in parallel with any two patient cable leads.

*Reset Recovery* Automatic return to on screen within .5 seconds after an electro surgical or defibrillator overload.

Slew Rate: Internally limited at .2 to .25 mv/ms referred to input at nominal gain.

*Calibration Signal:* 1 mv +/-2.5% referred to input.

Output: High-level single-ended output on front panel. Output level dependent on gain setting.

Output Impedance: < 100 ohms
Output Dynamic Range: 3.5 volts +/- 10%

*Output Offset
<50 mv for DC input @ 25°C
<200 mv @ nom gain over full temp range

Output Current > +/- 5 ma

*Noise:
<5 uv RMS referred to input at ECG output with RA and LA connected to RL by shielded 25 Kohm resistors.
<50 uv RMS referred to input at scope display at nominal Gain setting.

Common Mode Input
>12 megohms from patient leads to Impedance: chassis ground, from DC to 50 Hz.

5.3 SOLID TRACE SCOPE

Viewing Area: 3.94" wide x 3.15 high (8x10 cm)

*Gain
.33 mv/cm to 3.3 mv/cm from patient leads to scope display depending on ECG amplifier gain setting.

Brightness: Internal adjustment.

Sweep Speed: 25 mm/sec. +/-5%

Warm-up: Visible in 15 seconds.

Memory Time: 4 seconds visible

Sample Rate: 240/sec.

Resolution: 8 bits

Phosphor: P31

Refresh Rate: 60 Hz

*Transient Response: < 5 percent overshoot to step input of any magnitude up to full scale.
*Frequency Response:*.5 to 40Hz +0-3db max. from isolated input to scope display @ 1 cm deflection.

Horizontal Sweep Linearity: Better than 5% over full viewing area.

Vertical Linearity: Better than 5% over 6 cm central viewing area from isolated input to scope display.

Drift: Baseline will not drift more than .5 cm with 5 minutes after power turn on.

Sampling Noise: <.3 mm at any gain setting.
5.4 SYNCHRONIZED CARDIOVERTER

QRS Detector: Automatic threshold greater than .6 cm either polarity QRS complex.

*Sensitivity: < .3 mv at maximum gain setting

Range: 0-250 beats per minute.

QRS Tone: 1 KHz tone

Marker Pulse: Shown on scope +/-20 ms from beginning of counter shock.

*Discharge Delay: Energy is delivered within 40 ms of the R wave peak with proper gain setting.

5.5 HEART RATE METER

*Range 0-250 BPM

*Accuracy 3 BPM or 5% of reading whichever is greater.

Response Time: < 5 seconds for rates greater than 50 and an input step change of 70 BPM

Alarm Setting Accuracy: Better than +/-5 BPM

Alarm Delay: 3 Seconds +/-1 second

*Pacer Artifact Rejection: Will not respond to pacer spikes <= 4 ms with proper lead placement.

5.6 WRITER (D320W/400W only)

Linearity: 1% of full scale

*Frequency Response: .5 to 40 Hz +0, -3db maximum from isolated input connector at 1 cm deflection.

Chart Width: 40 mm

Chart Speed: 25 mm/sec +/-3%

5.7 DEFIBRILLATOR BATTERY SUPPLY

*Battery Life: Minimum of 5 hours of monitoring, 1.7 hr of monitoring with writer running, or 50 defibrillator charges at 320 joules, or any...
proportional combination at 25°C. 6 hours of monitoring or 60 shots typical.

Minimum of 5 hours of monitoring, 1.7 hrs of monitoring with writer running, or 40 defibrillator charges at 400 joules or any proportional combination at 25°C. 6 hours of monitoring or 50 shots typical.

Battery Type: NiCad 12 volt battery pack located inside unit.

14 hours to full charge

Comes on when minimum of 1/2 hour of monitoring or 2 charges to 320 joules of battery capacity left.

5.8 AC LINE REQUIREMENTS

Input Requirements

97/127 VAC 48-65 Hz, -01, -03, -05, -07
194/254 VAC 48-65 Hz, -02, -04, -06, -08

Power Requirements:

55 watts max, with fully discharged battery in charge mode.

Green Wire Leakage:

<50 ua RMS at 120 VAC 60 Hz measured with AAMI load.

Hipot:

2500 VAC RMS 60 Hz between AC hot and neutral and green wire ground.

5.9 PADDLES

Electrode Finish:

<250 micro inches RMS surface roughness.

Electrode Material

400 series stainless steel.

Handle Material:

Flame resistant plastic

5.10 PHYSICAL CHARACTERISTICS

5.10.1 Size: 17.81" x 15.10" x 8.94"

45.24 cm x 38.35 cm x 22.54 cm

Weight: 33 lbs. (-01, -03, -05, -07)

37 lbs. (-02, -04, -06, -08)
5.11 ENVIRONMENTAL CHARACTERISTICS

5.11.1 Temperature
- Operating: -10°C to 55°C (14°F to 131°F)
- Storage: -25°C to 55°C (-13°F to 158°F)
- Notes: Continuous battery charge over 40°C ambient reduces battery life. Long term storage over 50°C reduces battery life.

5.11.2 Humidity
- Operating: 5% to 96% relative humidity
- Storage: 5% to 80% relative humidity

5.11.3 Atmospheric Pressure
- 70 kPA to 103 kPA

5.11.4 Shock and Vibration
- Shall comply with the shock and vibration requirements of section 3.2.3 of the XXX Cardiac Defibrillator Standard, document number XXX-XXX-021-0001.

Sheet 1 of 1

TITLE: IN4278 ZENER DIODE SPECIFICATION NUMBER

Drafted by App. Date

REV. ECN History Notes Date

1. SCOPE: This specification describes a one-watt zener diode used for voltage reference in the XYZ Stimulator.
2. ELECTRONIC CHARACTERISTICS

2.1 Zener Voltage: 3.1 vdc @ 76 madc

2.2 Maximum Zener Impedance: 10 ohms @ 76 madc

2.3 Reverse Leakage Current: (25%) 100 microamps (max) @ 1 vdc

3. TESTING: All diodes shall meet the requirements of JANTX IN4278 as specified in MIL-S-19500/127G.

4. PHYSICAL CHARACTERISTICS

4.1 Diodes shall be packaged in a void-free silicone case.

4.2 Leads shall be readily solderable.

5. MARKING

5.1 The cathode shall be identified by a color band.

5.2 An identification number and lot number or date code shall represent a specific manufacturing period.

5.3 All markings shall be permanent such that cleaning solutions will not remove the markings.

6. CERTIFICATION

6.1 A certification of compliance with this specification and a test data sheet must accompany each lot shipped.

6.2 Certification must include a statement that no changes have been made in materials or physical or electrical characteristics.

7. APPROVED SUPPLIERS

7.1 XXXXXXXXXXXXXXXXXXXXXX

XXXXXXXXXXXXXXXXXXXXXXXXX
HAND-SWITCHING PENCIL

STERILE REUSABLE

Catalog No. E2502B

STERILITY GUARANTEED UNLESS PACKAGE HAS BEEN DAMAGED OR OPENED:

CONTENTS:

One sterile reusable Hand-switching Pencil with 10 fölt cord and plug and disposable blade electrode. Accepts all standard 3/32" shaft electrodes.

DIRECTIONS:

1) Open package by peeling apart at arrow.

2) Remove LectroSwitch®Pencil from sterile package using aseptic technique. Do not permit LectroSwitch®Pencil to contact unsterile end of package or any object outside the sterile field.

3) Check blade electrode connection for secure fit prior to use

4) Insert plug connection into active hand-switching receptacle on generator. An adapter may be required for generators not manufactured by Valleylab, Inc.

5) Remove protective sleeve from blade electrode.

CAUTION: AFTER USE THE LECTROSWITCH®PENCIL MUST BE STERILIZED. DISCARD THE DISPOSABLE BLADE ELECTRODE BEFORE REPROCESSING. RECOMMENDED STERILIZATION TECHNIQUE IS SHOWN ON PACKAGE INSERT IN BOX CONTAINING LECTROSWITCH®PENCILS.

NOTE: GOOD OPERATING ROOM PRACTICE SUGGESTS THAT ACTIVE ACCESSORIES BE PLACED AWAY FROM THE PATIENT WHEN NOT IN USE.
NOTES:

1. WHEN ASSEMBLING HANDLE ASSY TO SCOPE 1,
   TIGHTEN NUT ITEM 8 SUFFICIENTLY SO THAT IT REQUIRES EIGHT (8)
   TO NINE (9) POUNDS OF FORCE TO ROTATE HANDLE WHEN AS
   SHOWN IN FIG. 1.

2. AFTER THIS TEST, ROTATE HANDLE BACK & FORTH SEVERAL TIMES & TEST
   AS IN STEP 10. TIGHTEN NUT IF NECESSARY & REPEAT STEP 12.
   IF NECESSARY UNTIL PROPER TORQUE IS ACHIEVED.

3. USE CHATILLON MODEL 86P-25 STRAIN GAUGE OR EQUIVALENT.

PART LIST

<table>
<thead>
<tr>
<th>PART LIST</th>
<th>PART NO.</th>
<th>ITEM</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>24990096</td>
<td>MAT.</td>
<td></td>
</tr>
</tbody>
</table>

HANDLE ASSY

DIMENSIONS ARE IN INCHES
TOLERANCES SAME AS DRAWING

SEE PL 19900096

SCALE 1-1
<table>
<thead>
<tr>
<th>ITEM NO.</th>
<th>SIZE</th>
<th>PART NO.</th>
<th>DESCRIPTION</th>
<th>REF.DES.</th>
<th>QTY.PER.TAB NO.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITEM NO.</td>
<td>SIZE</td>
<td>PART NO.</td>
<td>DESCRIPTION</td>
<td>REF.DES.</td>
<td>QTY.PER.TAB NO.</td>
</tr>
<tr>
<td>---------</td>
<td>------</td>
<td>----------</td>
<td>-------------</td>
<td>----------</td>
<td>----------------</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.02</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
Cat. XXXXXX

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.110</td>
<td>PS 02-0002 Bottle</td>
</tr>
<tr>
<td>3.111</td>
<td>PS 02-0102 Cap</td>
</tr>
<tr>
<td>3.112</td>
<td>PS 05-0007 Teflon liner</td>
</tr>
<tr>
<td>3.113</td>
<td>PS 02-0701B Label</td>
</tr>
<tr>
<td>3.114</td>
<td>PS 03-0707 Instruction sheet</td>
</tr>
<tr>
<td>3.115</td>
<td>PS 03-0301 Boxes</td>
</tr>
<tr>
<td>3.116</td>
<td>PS 03-0002 Platforms</td>
</tr>
</tbody>
</table>

3.2 XXXXXX Production

3.201 SOP-XXXXX Filling, labeling and packaging

4. Quality Control Specifications

4.1 Raw Material Specification (RM)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.101</td>
<td>RM 01-0002 XXXXXXXXXX</td>
</tr>
<tr>
<td>4.102</td>
<td>RM 01-0003 XXXXXXXXXX</td>
</tr>
<tr>
<td>4.103</td>
<td>RM 01-0005 XXXXXXXXXX</td>
</tr>
<tr>
<td>4.104</td>
<td>RM 01-0007 XXXXXXXXXX</td>
</tr>
<tr>
<td>4.105</td>
<td>RM 01-0008 Sodium Hydroxide</td>
</tr>
<tr>
<td>4.106</td>
<td>RM 01-0012 XXXXXXXXXX</td>
</tr>
<tr>
<td>4.107</td>
<td>RM 01-0017 Hydrochloric XXXXXXXX</td>
</tr>
<tr>
<td>4.108</td>
<td>RM 01-0004 Sodium Chloride</td>
</tr>
<tr>
<td>4.109</td>
<td>RM 01-0001 Bottle (3200-01)</td>
</tr>
<tr>
<td>4.110</td>
<td>RM 01-0002 Bottle (3200-10)</td>
</tr>
<tr>
<td>4.111</td>
<td>RM 01-0101 Cap (3200-01)</td>
</tr>
<tr>
<td>4.112</td>
<td>RM 01-0102 Cap (3200-10)</td>
</tr>
<tr>
<td>4.113</td>
<td>RM 02-0701A Label (3200-01)</td>
</tr>
<tr>
<td>4.114</td>
<td>RM 02-0701B Label (3200-10)</td>
</tr>
<tr>
<td>4.115</td>
<td>RM 03-0001 Boxes (3200-01)</td>
</tr>
<tr>
<td>4.116</td>
<td>RM 03-0002 Platform (3200-10)</td>
</tr>
<tr>
<td>4.117</td>
<td>RM 03-0301 Boxes (3200-01)</td>
</tr>
<tr>
<td>4.118</td>
<td>RM 03-0320 Boxes (3200-10)</td>
</tr>
<tr>
<td>4.119</td>
<td>RM 03-0701 Instruction sheet (3200-01)</td>
</tr>
<tr>
<td>4.120</td>
<td>RM 03-0707 Instruction sheet (3200-10)</td>
</tr>
<tr>
<td>4.121</td>
<td>RM 05-0006 Teflon liner (3200-01)</td>
</tr>
<tr>
<td>4.122</td>
<td>RM 05-0007 Teflon liner (3200-10)</td>
</tr>
<tr>
<td>4.123</td>
<td>RM 01-0001 XXXXXXXXXX</td>
</tr>
</tbody>
</table>

4.2 In-process Specifications

4.201 SOP-58200B-0 Optical Density of XXXXXXXX substrate

4.3 Final specifications

4.301 QC-PB-007 Finished goods quality control-XXXXXXX set

5. Final Release

5.1 Final Release Specification

5.101 #1087 Final Product Release Form
1. PRODUCT SPECIFICATION FOR AMYLASE, CATALOG NO. 3200

1.1 Product name: Amylase Set

1.2 Description of product

This Amylase Set is used for the quantitative determination of amylase in biological fluids.

The principle of the procedure is as follows:

Starch + H₂O amylase > colorless starch fragments

Unhydrolyzed Starch + I₂ ----> colored starch-iodine complex

The color produced by the starch-iodine complex after 7.5 minutes incubation of substrate with specimen and 15 minutes color development is compared with a reagent blank. The decrease in absorbanceoptical density (OD) at 660 nm is proportional to amylase activity in the specimen because the enzyme hydrolyzes starch to fragments that do not react with the iodine reagent.

1.3 Product availability

Catalog No.: 3200-01

Catalog No.: 3200-10

1.4 Components of product

Catalog No. 3200-01

15 Tubes of lyophilized substrate

1 Bottle (10 ml) Iodine (.OIN)

1 Instruction sheet
Catalog No. 3200-10

100 tubes lyophilized substrate

2 Bottles (30 ml ea.) Iodine (.OIN)

1 Instruction sheet

1.5 Storage of reagent

Store at room temperature. Do not refrigerate.

Minimum shelf life is one year.

Do not use any substrate tube in which moisture is observed.

1.6 Stability of specimen

Amylase activity in serum is stable up to one week at room temperature and for one to two months if refrigerated at 2 to 8°C.
1.7 Procedure for urine amylase

Collect a timed (minimum of 2 hours) sample of urine and measure the volume. Follow the same procedure as used for serum amylase. Calculate the amylase activity excreted in the urine per hour as follows:

\[
\text{Urine amylase (unit/hour)} = \frac{OD_{\text{Reagent blank}} - OD_{\text{Specimen}} \times IOV/H \times Tf}{OD_{\text{Reagent blank}}} \\
V = \text{total volume of timed urine specimen in milliliters}; \\
H = \text{total collection time in hours}; \\
Tf = \text{temperature correction factor}.
\]

Example:

2 hour volume of urine = 130 ml;
OD blank = 0.57;
OD Specimen = 0.48;
Temperature = 37°C;

\[
\text{Urine amylase (unit/hour)} = \frac{0.57 - 0.48 \times 10 \times 130 \times 1}{0.572 \times 2} = 103
\]

Caution: Some urine specimens may contain reducing substances which could exhaust the iodine reagent.

1.8 Units

One amylase unit is defined as that amount of enzyme activity which, under the conditions of this procedure, will hydrolyze 10 mg of starch in 30 minutes to a stage at which no color is generated with iodine.

1.9 Normal Range

Normal range for serum is 50 to 200 units at 37°C. Infants below two months have no measurable serum amylase. Adult level is reached by the age of one year. The above normal range includes an average serum blank of 25 amylase units. Normal values for urine is less than 375 units per hour at 37°C.
1.10 Precision

Coefficient of variation of 5 to 6 percent at a level of 120 units and 3 to 5 percent at a level of 250 units are obtained with good laboratory technique.

1.11 Performance characteristics

This assay measures amylase levels up to 500 units per 100ml specimen in a linear manner. Specimens with higher activity must be diluted by the procedure given in Note 2 [not reprinted in this manual]. The calculated value includes a serum blank, which averages about 25 units in human sera. Control sera may have larger serum blanks, often up to 100 units. Values obtained on patient sera when corrected for the serum blank activity of approximately 25 units are very close to the values obtained by the Somogyi Saccharogenic method.

1.12 Cautions

This product must be protected from contamination by amylase. Saliva is a very potent source of amylase. Perspiration contains some amylase as do other body fluids. Insensible droplets of saliva are projected during speech, sneezing, etc.

Face masks and hair covering must be worn during solution and diluent preparation, solution filling, tube racking and capping, and when handling any raw material defined for use with this diagnostic test.

Equipment used in the procedure should be designed "For Amylase Only". Glassware and other equipment suspected of amylase contamination must be rinsed with XXXXXXX. Avoid contamination with detergents or soap. (See SOP #G021). Observe safety precautions when handling acids (SOP #G022).

1.13 Manufacturing Flow Sheet.

See Form No. 9926. [Not reprinted in this Manual].
MASKS MUST BE WORN THROUGHOUT THIS PROCEDURE TO PREVENT SALIVA CONTAMINATION.

FOR 50 LITERS OF AMYLASE DILUENT SOLUTION:

1. Weigh the following chemicals and place them in 43 liters of deionized water in a calibrated clean container.

DEIONIZED WATER: Source ______ Vol. _______ml Done By _______________________

Conductivity Light: On _______ Off _______ Checked By _____________________________

VENDER LOT AMOUNT WEIGHED

CODE NO. REQ'D WEIGHT BY BY

RM. NO. CHEMICAL

__________________________________________________________________________________

01-0004 Sodium Chloride _____ _____ 425.0 g G ____ _____ _____

±0.1 T ____

N ____

01-000X XXXXXX _____ _____ 523.25 G ____ _____ _____

Basic _____ _____ ±0.1 T ____ _____ _____

N ____

01-000X XXXXXX _____ _____ 1275.0 g G ____ _____ _____

Basic _____ _____ ±0.1 T ____ _____ _____

N ____

Note: Slowly add the sodium XXXXXXXX to prevent caking.
2. Stir the diluent until all of the salts go into solution.

Done by ____________________

3. Check the pH of the solution against 7.00 pH reference buffer.

Initial pH ________________ Checked by ____________________

4. Adjust the solution to a pH of 7.00 ± 0.05 @ 25°C using 2N NaOH

mls of _____ -- used. Lot No. _______ pH _____ @ 25°C

Checked by ____________________

5. Add 125 mls of 1% XXXXX solution & mix well. Done by ____________________

No. of mls added ____________ Supplier __________________ Lot No. _________________

6. Bring the volume to 50 liters with deionized water and mix well. Re-check the pH. It should still be 7.00 ± 0.05 @ 25°C. Adjust, if necessary, with 2N NaOH or 6N HCl.

DEIONIZED WATER:

Source ________________ Final Vol. _______ mls. Done by ________________

Conductivity Light: On ______ Off _____________ Checked by ____________________

mls of _____ used to adjust. Lot No. ______ Done by ________________
7. Solution must be approved by the Solutions Supervisor(s) or their designee before it can be used. Approved by: __________________ Date __________________

8. The Solution is now ready to be used in the preparation of Amylase.

It will be filtered as it is during that preparation.

9. Label the Diluent Solution with the **Product Name**, **Batch Number**, and **Date** of Manufacturing.

PROCEDURE  Amylase Diluent Solution No. _______________  Rev. _______________

Form No. 1084 Sheet 1 of 1

**FILLING RECORD** - Liquid, Non Freeze Dried

Product Name _______________________________  Kit Cat. # _______________________

Distributor _______________________________  Kit Lot # _______________________

Theoretical Tube & Vial Yield _________________________  Kit Exp. Date _________________________

**SPECIAL INFORMATION** ________________________________

**IODINE**

Batch # __________________________  Date Manuf. __________________________

Date Received _______________  Time Received __________________________

**TUBE AND VIAL** Code # ___________________________  # Racked

**INFORMATION**  # Lost ___________________________  Total # Used
FILLING DATA

Machine(s) Before Filling - Signed __________________ Date _________________

Cleaned:

After Filling - Signed __________________ Date _________________

Fill Vol. ______ ml Limits ± _____ ml Filling ___________________________

Batch Vol. ______ ml Leftover ________ ml Method __________________________

# Tubes or Vials Filled ______ #Bad Fills ______ [ ] Refilled

[ ] Not Refilled

APU _______________ ml TPU ml _______________ TPR ml _______________

Filling Operators 1) _____________ 2) _____________ 3) _____________ 4) _____________

Volumetric Fill Checks: 1) _____________ 2) _____________ 3) _____________

4) _____________ 5) _____________ 6) _____________ 7) _____________ 8) _____________

Checks done by _______________________________________ Date ____________________

CAP AND LABEL INFORMATION

1. Cap Code # ___________ # Used ___________ # Lost ___________

2. Cap Code # ___________ # Used ___________ # Lost ___________

Label Code # ___________ # Used ___________ # Lost ___________

Signed _______________________________________ Date _________________

Checked by ________________________________ Date _________________
## ATTACH SAMPLES OF LABELS

<table>
<thead>
<tr>
<th>FINISHED PRODUCT RELEASE</th>
<th>Form No.</th>
<th>Rev.</th>
<th>Sheet 1 of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form Approved by:</td>
<td></td>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>ECN notes:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Title: AMYLASE SET

| Packaging lot number | Circle one CATALOG Number → AM-389-01 AM-389-02 |

The device history documents below were reviewed by →

Circle one form number in 2, 5 & 7 below.

1. Form # 9926 Product flow sheet
2. Form # 1077 or 1078 Iodine solution
3. Form # 1082 Substrate solution
4. Form # 1083 Substrate tube filling sheet
5. Form # 1084 or 1085 Iodine filling sheet
6. Form # 1086 Packaging record
7. Form # QC-PP-07 or QC-PP-01 Finished device specification

**Comments**

Sign. MFG Designee APP. Yes or No → xxxxxxxxxx

**Comments**

Signature QC Designee Approved Yes or No

### Production Workmanship and Configuration Sample Tag

<table>
<thead>
<tr>
<th>PRODUCTION SAMPLE NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUMENT/PART NUMBER</td>
</tr>
<tr>
<td>SAMPLE NUMBER</td>
</tr>
</tbody>
</table>

NOTES:
### APPROVED FOR USE BY:

<table>
<thead>
<tr>
<th>Role</th>
<th>Signature Required</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROJECT ENGINEER</td>
<td>Signature Master Sample Only</td>
<td>DATE</td>
</tr>
<tr>
<td>LEAD ASSEMBLER</td>
<td>Signature all samples</td>
<td>DATE</td>
</tr>
<tr>
<td>LEAD TECHNICIAN</td>
<td>Signature all samples</td>
<td>DATE</td>
</tr>
<tr>
<td>PRODUCTION MANAGER</td>
<td>Signature master sample only</td>
<td>DATE</td>
</tr>
</tbody>
</table>

Back of Sample Control Tag (the above tag)

### SAMPLE MODIFICATION HISTORY

<table>
<thead>
<tr>
<th>Modification Number</th>
<th>ENG (MASTER ONLY)</th>
<th>LEAD ASSEMBLER</th>
<th>LEAD TECHNICIAN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIGNATURE</td>
<td>DATE</td>
<td>SIGNATURE</td>
</tr>
</tbody>
</table>

### SHOP ORDER TRAVELER

<table>
<thead>
<tr>
<th>Form 058-SOT</th>
<th>S.O.T. NUMBER</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Part No.</td>
<td></td>
</tr>
<tr>
<td>FROM Department</td>
<td>TO Department</td>
<td></td>
</tr>
<tr>
<td>Quantity Delivered</td>
<td>Quantity Accepted</td>
<td></td>
</tr>
<tr>
<td>Supervisor</td>
<td>Supervisor</td>
<td></td>
</tr>
<tr>
<td>Remarks</td>
<td>Lot No. Complete Thru OPN</td>
<td></td>
</tr>
</tbody>
</table>

### FOLLOWER TAG

<table>
<thead>
<tr>
<th>Instrument Name</th>
<th>Model No.</th>
<th>Form 092-FT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROCESS</td>
<td>BY EMPLOYEE</td>
<td>DATE</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------</td>
<td>------</td>
</tr>
<tr>
<td>Assembled</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-process Check</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chassis Check</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test &amp; Calibration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burn-in</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Audio Calibration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final In-process Inspect.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seal Card Cage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Cover Inspection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Assembly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Inspection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packing/Shipping Inspect.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Updated 1/1/1997
9. Document and Change Control

INTRODUCTION

There is no easy way to properly control changes to devices, processes, device master records, etc. Change control is a complex process. Failure to have an adequate change control system can cause equally "complex" results. Inadequate change control exposes a company to product liability actions, results in product recalls, causes internal confusion, and is a serious violation of the Quality System (QS) regulation.

Change control activities and procedures apply to: design; components, including software; labeling and packaging; device manufacturing processes; production equipment; manufacturing materials; and all associated documentation such as quality system procedures, standard operating procedures, quality acceptance procedures and data forms, and product-specific documentation. Change control should also be applied to any production aids such as labeled photographs and models or samples of assemblies and finished devices.

The device master record (DMR) is a compilation of records containing the procedures and specifications for a finished device [820.3(j)]. This record contains the manufacturer's documentation for the device specifications and all other documentation required to procure components and produce, label, test, package, install, and service a finished device. Manufacturers are to prepare, control changes to, and maintain a device master record using the document controls procedures outlined in 820.30 and 820.40.

CHANGE CONTROL PROCEDURE

Changes to DMR documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval unless there is a specific designation that states otherwise. These approved changes shall be communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include:

- a description of the change,
- identification of the affected documents,
- the signature of the approving individual(s),
- the approval date, and
● when the change becomes effective [820.40(b)].

For the medium to large company, a change control procedure is one of a family of standard operating procedures (SOP's) used to produce and control documentation or control activities that result in documentation. The sample engineering change policy/procedure exhibited at the end of this chapter lists a group of six such procedures. However, this chapter concentrates on only one of these -- the change control procedure -- because of the specific requirements for change control in the QS regulation. It is a traditional and current practice for change control procedures to include change control forms. Some manufacturers also use change request forms for suggested changes.

The written change control procedure should describe the company-approved procedures to be followed from the time parts of the device master record are first released for production through examination of a change in relation to other appropriate documents, activities, and implementation. The company procedure should have an appropriate degree of flexibility integrated into it. That is, all changes do not need the same degree of evaluation and approval. Consider manufacturers such as repackers/relabelers that may have to make simple changes such as the size of a container or arrangement of the items in a kit. Also, production runs for some kits may last only a few hours. Obviously, these manufacturers should develop and use a change control procedure that allows rapid changes, approvals, and implementation. The QS regulation is a flexible regulation which allows manufacturers to develop and use procedures that meet their specific needs.

The important point to consider is that all changes are made according to the approved company policy and procedure. A trap that is easy to wander into is the situation where a company, knowingly or unknowingly, allows research and development personnel or other appropriate technical personnel to make changes to a device that is already in production or make changes to an ongoing process without following the approved procedure. Such changes generally do not receive the necessary evaluation and review and, therefore, they may and in many instances have resulted in hazardous or ineffective devices. Making uncontrolled changes is a violation of several sections of the QS regulation, including sections 820.30, 820.40, 820.70, 820.75, and 820.181. Also companies making uncontrolled changes are not operating in a state-of-control. It bears repeating: all changes should be made according to the approved company policy and procedure.

A change control procedure may be long when a large number of activities are covered. However, a very small manufacturer may have only a few activities. For very small manufacturers, the following are some examples of how to word simple procedures for changing and approving the device master record:

- Draw a line through but do not black out the old information.
- Ink in the new information.
- Date and sign at the change or place a mark at the change which refers the user to the date and signature.
- Ascertain that the modified documents are placed into use and the old documents are removed from production.
- Record the effective date for these procedures.

The above procedure obviously depends on the devoted attention and knowledge of the person responsible for the change. It is obvious that for a large manufacturer or for complex operations, the person responsible for the change would not or could not "pass the word" to everyone that has a need to know. Hence, the need for written procedures. Small manufacturers, with short communication lines, usually need a less extensive procedure than a large manufacturer; however, the use of a change control form, as described below, by small manufacturers is highly recommended. As the manufacturer grows, all procedures, particularly the change control procedure, should be analyzed and modified to meet current needs. Such a review should be part of the quality system audit.

Change control records for documents should cover:

- identification of the entity being changed,
- a description of the change,
- identification of the affected documents,
- signature of the approving individual(s),
- the approval date, and
- when the change becomes effective.

These elements of a typical change control system are explained below. These controls extend to installation and service when a manufacturer is performing, or contracting these activities.

Identification

The written procedure should cover the identification of the changed device, assembly, component, labeling, packaging, software, process, procedure, manufacturing material and any other related item or document. The change control form should have blanks for recording this data and other data discussed below.

Effective Date

The procedure shall cover the effective date of the change which is usually a completion date, or an action to be performed when a specific event occurs, such as "implement the change when the new mixer is installed, validated, and
Responsibility

The change control procedure should state which department or designee is responsible for each function to be performed. One of these is the issuance, use, and control of blank and completed change control forms. Another is the extra level of management oversight during the phase-in of a change. (Also see Document Distribution below.)

Revision Level

The way the revision level is to be incremented and which code should be used need to be covered by the change procedure for: components including software, assemblies, and devices; and associated documentation such as labeling, process procedures, and assembly drawings. It is common practice to use numerical revision levels during pilot production and letters during full scale production.

Validation

Each changed device, accessory, labeling, packaging, and process should be thoroughly verified and/or validated by the appropriate department. Then the test results and all information related to the change should be reviewed by the change control board or other designated review group. This procedure is the same as needed for designing and introducing a new product or process into production and is detailed in section 820.30, Design Controls. Changes that only modify documents and do not change any design aspect of a device or process are performed according to 820.40 Document Controls. The change control procedure should state the details of the evaluation and review process or, as appropriate, refer to the company control procedures. The change control procedure should define the responsibilities of the various departments and members of the review board.

Communication

The change procedure should cover the communication of changes to all affected parties such as production, purchasing, contractors, suppliers, etc. As appropriate, activities that apply to internal operations are also applicable to suppliers. Examples are employee training, rework, or disposition of in-process assemblies, use of revised drawings and/or procedures, and disposition of old documents.

Updating Documentation

The change procedure should cover updating of primary and secondary documentation such as instruction manuals. Usually there are no problems with updating or revising primary documentation -- in fact, that is a major reason the given change order is being processed. In contrast, it is rather easy to forget that related secondary documents such as component drawings, instruction manuals or packaging require revision if affected by a given change. The use of a good change control form can alleviate this problem.

Documentation Distribution

Revised documentation should be distributed to persons responsible for the operations affected by the change and old documents removed and filed or discarded, as appropriate. After a document has been approved, these documents shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use. This means current documentation shall be accessible to company employees [820.40(a)]. Supervisors should be vigilant in overseeing the flow and use of documentation, especially if a change is being phased in, because both the old and revised documentation may exist in a given department during the transition period.

Remedial Actions

Certain changes may affect installation or servicing, or require remedial action in the field or rework of warehouse stock. Changes of this nature should be addressed in the change control procedure. The change control procedure should outline the documentation and activities required for changes involving installation, servicing, or field remedial actions or rework of warehouse stock. (Note that field remedial actions may be classified as recalls depending on the nature of the change. Generally, rework of warehouse stock which is under a manufacturer's control is not classified as a recall.)

Regulatory Submissions

Modifications to devices or manufacturing processes should be made and covered under the quality system change control procedure as described herein. Such changes may also require a premarket notification [807.87(g)] or premarket approval (PMA) supplement (814.20) depending on the classification of the device. The change order or control form is a convenient document for reminding employees that regulatory submissions should be considered when making a change.

Business Factors

In order for the change procedure to be complete, it should also cover other factors such as financial impact, modification of sales literature, update of products in commercial distribution, etc.

QUALITY ASSURANCE REVIEW

Identifying the need for change; making, evaluating, and reviewing the change in the product or process; and revising and distributing the documentation is about half of the change control process--the change also needs to be
Quality assurance and other designated personnel should make certain that the change is fully implemented during routine production, as shown by data and activities that meet GMP requirements for:

- review of production records [820.80(d)(2)];
- acceptance of components, labels, materials, etc. [820.80];
- assuring that quality assurance checks are appropriate and adequate for their purpose and are performed correctly [820.30(d), 820.181(c) and 820.80(d)(1)];
- finished device evaluation [820.80(d)];
- collection of device history record data to demonstrate that the device is manufactured in accordance with the updated device master record [820.184]; and
- making certain that only accepted product is distributed, used, or installed [820.80(d) and 820.86].

The change procedure should cover these activities and specify that they are accomplished before the first lot of the changed devices is released for distribution. After the change is implemented, resulting components, in-process items and finished devices should meet the new specifications established in the revised DMR as shown by the data in the Device History Record. This agreement, of course, is assured by the change control procedure as well as the remainder of a manufacturer's quality system.

**CHANGES UNDER PREMARKET NOTIFICATION**

When making changes to devices and associated manufacturing processes for substantially equivalent devices, manufacturers should consider both Subpart E of Part 807, and Part 820 of Title 21, Code of Federal Regulations, which address Premarket Notification Procedures and Good Manufacturing Practices for Medical Devices, respectively. By considering these simultaneously, labor costs can be reduced and compliance enhanced.

**Regulatory Background**

Under the Act, the burden is on the manufacturer to determine whether a premarket notification should be submitted for a change or modification in a device. It is not intended that the owner should submit a premarket notification for every change in design, material, chemical composition, energy source, or manufacturing process. Rather it is the manufacturer's responsibility to determine if a proposed change could significantly affect safety or effectiveness. If this change will affect safety or effectiveness, another Premarket Notification submission [510(k)] shall be submitted to FDA. (Please see Premarket Notification 510(k): Regulatory Requirements for Medical Devices, FDA 95-4158 and Deciding When to Submit 510(k) for a Change to an Existing Device.)

Changes in manufacturing processes, labels, packaging, device master record, design, etc., of a device are also subject to GMP requirements in sections 820.30, 820.40, 820.70, 820.75, 820.90, and 820.181. Compliance of manufacturers with these change-control requirements is checked during comprehensive inspections by FDA investigators. Manufacturers may consider their degree of compliance with the QS regulation as one factor, but not the sole factor, when making decisions about premarket notification submissions for modified devices or processes.

**Premarket Notification Decisions**

Premarket notification submissions are required for changes that could significantly affect safety or effectiveness and for new or modified intended uses. Additional submissions are not required for marketing or convenience changes where safety or effectiveness could not be significantly affected. Management should decide whether or not a change meets the threshold requirements for submitting a new premarket notification. While waiting for an FDA review of the submission, a manufacturer may continue to distribute the unchanged device for its original intended use.

Some manufacturers with highly qualified personnel and substantial experience may feel confident in performing various technical operations and analyzing results to determine that a particular change in a device, component, or manufacturing process will not significantly affect safety or effectiveness of the device. After technical activities are completed and documented, the results should be reviewed by a design-review panel, change control board, or equivalent group. Reviewing changes should include design verification/validation, change control procedures, equipment qualification, equipment calibration, process validation, personnel training, and routine manufacturing procedures. If it is determined that the change(s) to a previously FDA cleared device could not significantly affect safety or effectiveness of the device, then the intent of the regulation has been addressed and there is no need to submit an additional premarket notification. If this thorough review of proposed changes indicates that a change will significantly affect safety and effectiveness, either positively or negatively then another premarket notification shall be submitted.

**Quality System Control Always Required**

Section 807.87(g) requires that a premarket notification submission "include appropriate supporting data to show that the manufacturer has considered what consequences and effects the change or modification or new use might have on the safety and effectiveness of the device." Regardless of whether a change is submitted under the 510(k) process, the change should be evaluated under the QS regulation and the associated data filed for an appropriate period of time (820.180) because demonstration of process effectiveness and use of adequate quality assurance acceptance criteria for finished device release are GMP requirements. Change control is also necessary to assure that a modified device or process results in a device that meets company quality claims. Otherwise, the device is adulterated according to Section 501(c) of the FD&C Act.

The above information applies to changes contemplated for devices and associated processes that are subject to premarket notification requirements. If proposed device and process changes are for devices subject to Investigational Device Exemption (IDE) requirements or Premarket Approval (PMA) requirements, then FDA approval should be obtained, in advance, by submitting a supplemental IDE or PMA.
EXHIBITS

An example of a detailed change control procedure and several change control forms are described below and exhibited.

Engineering Change Policy/Procedure

This example of a change control procedure is typical of those used by many manufacturers of electromechanical products. It includes all of the elements described in this chapter and may be used as a guide in developing a change control procedure for medical devices.

Change Control Forms

To aid in the daily use of a change control system, manufacturers often use two forms in conjunction with the change control procedure. Examples of these forms are printed after the sample change control policy/procedures. The first form is called a request for engineering action (REA) or a similar title -- it is a "technical suggestion box." The use of this form encourages all personnel to be involved in product and process improvement, allows management to assign priorities to various tasks, and tends to prevent lack of action. The second form is called an engineering change order (ECO), engineering change notice (ECN), or a similar title. For most manufacturers, the use of ECO paper or computer forms is essential for the implementation and control of all the many elements in a change control system. A log of changes is usually maintained for fast reference to old ECO's and for controlling the issuance of sequential numbers for new ECO's. Also, if used, the completed REA and ECO forms need to be filed as required by the QS regulation in §20.180.

One of the example forms, Engineering Change Package (ECP), is simply an ECO cover sheet for a group of ECO's. An example of a filled-in group change is included. It includes the completed ECP cover sheet and two completed ECO forms. The other three completed ECO forms noted on the example ECP are not reprinted.

The contents of any forms selected for use by a manufacturer and how to use them should be discussed with all affected departments. Manufacturers may use, if appropriate, the example forms as exhibited or modify them to meet their specific needs. In either case, after using an ECO procedure and forms for a few changes to products, processes, and associated documentation, improvements to the form or procedure will become obvious if needed to meet the needs of a specific operation of a company.
3.0 APPLICABILITY: The responsibilities and procedures established by this policy shall apply to all released documents. The policy becomes effective immediately upon approval by the President.

4.0 APPLICABLE DOCUMENTS: The latest revision of the following documents form a part of this policy to the extent specified herein:

No. xxx Document Control Policy/Procedure
No. xxx Document Part Number Policy/Procedure
No. xxx Interchangeability/Compatibility Policy/Procedure
No. xxx Obsolescence Policy/Procedure
No. xxx Change Request Policy/Procedure
No. xxx Design Review Policy/Procedure

(Copies of these procedures and the ECO form discussed below are not included in this Manual. The REA form is reprinted at the end of this procedure.)

5.0 DEFINITIONS

5.1 Engineering Change Board: Each Engineering Change Board Member will represent a major area of activity. The Board will be under the direction of a moderator appointed by the President. The Change Board will meet to review the technical content of all proposed changes to released documentation for accuracy and impact on safety, efficacy, reliability, product cost, parts and finished goods inventory, work-in-process, instruction and service manuals, data sheets, test procedures, product specifications, compatibility with existing products, and other factors listed in ________section of Design Review Procedure No. _____________.

5.2 Change Request: A request for engineering action (REA) may start the change activities. The next stage is the completion of an engineering change request. An engineering change request (ECR) is a completed engineering change order form filled out as described in this policy but unsigned by the Change Board (i.e., is, it is an unsigned ECO form -- there is no ECR form in our company). To merit consideration by the Board, the change request must be complete. Unless the change is so simple that it can be readily understood from the Engineering Change "Request" form, the form must be accompanied by a reproducible copy of the last released revision of each sheet of documentation from the device master record that will be affected by the ECR if it is accepted. The reproducible copy must be marked with all proposed changes.

5.3 Engineering Change Order (ECO): An ECO is an ECR (that is, the completed ECO form and associated documents) which has been approved by the Engineering Change Board. An ECO must present a statement of the problem, a solution, updated documentation, an effective date, and a statement that the device and proposed changes meet regulatory requirements.

5.4 Regulatory Compliance: The review by the Change Board includes an analysis of the change with respect to regulatory requirements. For example, the following questions should be answered.

1. Is the change significant enough to require a 510(k) submission?
2. Is there a major change in the intended use? [Requires a 510(k).]
3. Does the change affect our quality system? (A new use such as infusion pumping by an existing precision metering pump means additional GMP requirements may apply.)
4. Do we need to change the labeling in order not to be misbranded?

5.5 Disposition: This action statement defines the updating or disposition of nonconforming materials, components, labeling, software, in-process assemblies, and finished devices at all applicable locations such as suppliers, stockroom, production lines, final test area, finished goods storage, and in field service.

5.6 Effective Date: The effective date will be expressed in terms of shipment date. That is, every change shall be applicable to all units shipped after a specific date. If shipment does not occur by the date specified, an amendment must be issued. The amendment will be presented to the Change Board and upon approval, the ECO cover sheet will be reissued. Quality Assurance has responsibility for verifying that the effective date is met as specified and for maintaining records showing the actual effective date of each change. If a change is not effective by the date specified, Quality Assurance shall be responsible for requesting an amendment to change the effective date.

5.7 Cost: At the Change Board meeting, each department shall be prepared to give the cost impact on its area for implementing each change order. Finance shall assure that all financial implications are considered because the cost analysis must include engineering time, manufacturing time and material, and field service material and labor. The following cost data is to be available at the meeting.
1. Amount of increase or decrease in per unit unburdened material and labor cost. This cost change is not to include extraordinary costs of rework and scrap which are incurred only when the change is first phased in.

2. Total unburdened cost of material to be scrapped in each location indicated on the ECO form.

3. Total unburdened rework cost for all items requiring rework.

4. Total unburdened engineering manpower and material required to design, test and document the change.

5. Where rework or replacement of units in the field is involved, Field Service must indicate the proportion of costs to be charged to warranty expense.

5.8 Amendment: An amendment may be issued only to change the effective date or correct drafting errors in implementing the change order. Any Board Member may request that an amendment be issued.

5.9 Board Member: An Engineering Change Board Member shall be a person appointed by the area manager to represent a particular functional area. A Board Member may represent more than one functional area. For changes to a process, or design of a device, labeling, or packaging, board members must at least include a design review to meet the following GMP requirements:

- Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development.

- The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed, as well as any specialists needed.

- The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file [820.30(e)].

5.10 Alternate: Each functional area shall also designate an Alternate who shall be available to attend Change Board meetings in the event that the Board Member is not available. Each functional area is to notify the Change Board Moderator of the names of its Board Member and Alternate.

6.0 RESPONSIBILITIES

6.1 Engineering Change Board Moderator: The Engineering Change Board will meet at the discretion of the Moderator. The Engineering Change Board Moderator is responsible for the conduct of the Change Board meetings. This person is appointed by the President for an indefinite term. At least one full working day before each meeting of the Change Board, the Board Moderator shall distribute to all Board Members a copy of all ECR’s to be discussed at the next meeting of the Board.

6.2 Engineering Change Board Members: Engineering Change Board Members shall be responsible for the functional areas they represent in all matters relating to engineering changes and shall be empowered to act on behalf of their areas in Board actions. The Board Members or Alternates shall come to each meeting thoroughly prepared to discuss each Engineering Change Request (ECR) to be discussed. Specific Board Member responsibilities are listed below.

Product Management - Product Management shall determine the effect of changes on marketability, field information, catalogs, price lists, data sheets, and gross profit margin. Product Management must verify the suitability of each design (not documentation only) change in the international as well as the domestic marketplace.

Field Service - Field Service has responsibility for determining the time required to implement the change in the field; availability of components and assemblies for retrofit; impact of the change on service manuals; and adjustments to service stock. Field Service will make the changes in the areas under their jurisdiction and pass other defined tasks to appropriate departments.

Quality Assurance - Based on verification data, analysis and design reviews, Quality Assurance and manufacturing engineering shall be aware of the effect of all changes on test requirements and on overall quality of our products and assure that product specifications are met. Quality Assurance shall assure that there is compliance with customer, corporate and regulatory agency requirements.

Manufacturing - Manufacturing shall determine component and raw material availability, break-in point, effect on material-on-order, material-in-process and material-in-stock. Manufacturing engineering shall assure that manufacturing and test procedures are adequate. Manufacturing shall determine total cost to the Manufacturing Department of implementing each change.

Engineering - Engineering is responsible for making certain that the change is technically feasible and complies with appropriate company and customer specifications and with accepted standards. Every major change must be fully analyzed and tested (verified) and the results documented by Engineering before it becomes a change order. Any Change Board Member may request that Engineering furnish evidence of technical viability of a change. If the Board so
decides, a change may be tried in Manufacturing on a limited pilot production basis before final approval and implementation in full-scale production. None of the trial units may be shipped until the change has been verified; validated, if appropriate; subject to design review; and received final approval. If, as the result of such trial production, the change is altered or modified before final approval, all of the trial units must be changed to the final form before shipment.

Engineering shall supply QA and Manufacturing Engineering with copies of verification protocols, if any, to be used to update production test methods. The updated production documents are part of the change.

**Finance** - Finance shall make certain that all financial aspects have been considered.

### 6.3 Engineering Documentation Section (Engineering Services)

Engineering Documentation Section shall have overall responsibility for coordinating, scheduling, and executing documentation changes.

---

**7.0 PROCEDURE:** The procedure followed for a given change depends upon whether the change is only to documentation or is a change that affects design, the manufacturing processes or just documentation.

#### 7.1 Procedure for Design and Process Changes

1. A request for engineering action (REA) is completed and forwarded to the Manager of Engineering Services. (The REA form is reprinted at the end of this procedure.)

2. A number is assigned and appropriate audit controls are established. Engineering Services then sends a copy of the REA to the cognizant device or process design section for recommended solutions, evaluation of impact on specifications, and a recommended effective date. As appropriate, the changes must be supported by device verification data and/or process evaluation data or validation data. The REA is then forwarded to the Engineering Documentation Section.

3. Upon evaluation for adequacy of data, where-used considerations for the items being changed are made. Engineering Services makes certain that the latest revision of all affected documentation is included. If not already done, an "ECR" (unsigned ECO) form is completed at this stage.

4. Sepias (or separate computer versions in a computerized system) are made of all affected documents. The ECR number and proposed changes are marked on the sepias. These sepias are included as part of the ECR. The only exception from this procedure is where the change is basically self-explanatory, i.e., where all necessary information can be discerned from the section on the ECR form indicating "change from" and "change to."

5. The Engineering Documentation Section will then duplicate and distribute copies of the ECR to each Change Board Member. Upon receipt of the ECR, each Member shall review the proposed change and determine the impact on their area.

6. The Change Board Moderator then calls a Change Board Meeting.

7. All aspects of the change request are reviewed at the meeting including the following: Is the ECR presented so that anyone may understand the problem and the solution? Does the verification data show that the device meets the device product specification? Does the device continue to meet the intended use and the needs of the user/patient? Has all documentation including manuals and data sheets been updated? The Board will then establish a reasonable effective date. Finance will make certain that all costs of this change have been considered. After agreeing upon an effective date, each Board Member signs the change request. Each signature implies concurrence with the method of solution, effective date, and costs. If the Board Members are unable to reach a unanimous decision, the issue is submitted to the President for resolution.

---

**Sheet 6 of 8**

After all Board Members in attendance have signed, the ECR becomes an engineering change order (ECO). Copies of the cover sheet may be issued by Technical Services upon request of the Board Members if the effective date is very near and the Change Board has not modified the ECR before approval. This action permits Manufacturing to use the previously distributed marked-up sepias or "from-to" information on the ECR as operating documentation until copies of the updated original documents are available for distribution.

It is the responsibility of Manufacturing to indicate the earliest permissible effective date in all areas, i.e., supplier, stockroom, raw material, and work-in-process. It is the responsibility of Field Service to indicate an effective date for any field activities.

8. The change order is then sent back to Technical Services where copies are made for the Board Members, who requested them. Upon completion of this task, the master documentation is withdrawn from the print file, updated to the new revision, and copies are distributed and obsolete documents are collected. During the updating process, a copy of the marked-up sepia (if any) replaces the master in the print file.

9. After all documents are updated, the change order is filed permanently in the design history file for the device. The verification protocol and data and design review documents and minutes are also placed in the design history file.
7.2 Procedure for Minor Changes and Changes in Documentation Only.

This procedure is the same as that for design changes except that the second and third steps read as follows:

2. A number is assigned and appropriate audit controls are established. Upon evaluation for adequacy of data, where-used considerations are made. Technical Services assures that all affected documentation is included and that it is the latest revision.

3. Technical Services then sends a copy of the ECR to the Design Section for evaluation of the effect of the changes on the device and for recommendations on the effective date to be suggested to the Change Board. The ECR is then returned to Technical Services.

8.0 ENGINEERING CHANGE ORDER FORM (ECO): A definition of the various items on the form and instructions on completing each item follows.

1. Status: At the top of the form are the words "Engineering Change" followed by two words, REQUEST and ORDER. When the mark appears in the request area or the form is not signed by the Board Moderator, it shall be considered a request or preliminary copy -- not an action copy. The change order is an action copy which must bear the signature of all Board Members or their Alternates. (The Moderator is empowered to sign for any function not represented at a meeting.)
   1. Amendments: Amendments shall be designated by an alpha suffix, e.g., A, B, C, etc.
3. Stock Room: What should be done with non-conforming purchased components in our stock room? By what date should the above action be complete?

4. Work-in-Process: What do we wish to do with the material on the floor?

5. Finished Goods: What do we do with the material in finished goods?

6. Field Service: What should be done to devices in the field?

7. Cost: Each department is responsible for reporting the cost of the change with respect to its area.

17. Effective Date: Each change shall be applicable to all units shipped after a particular date where the date is relatively unimportant because the change is a minor documentation change. In all other changes, an effective date must be assigned by the Board. If it is important to a particular functional area that a change be implemented by a date or not sooner than a date, it is the responsibility of the appropriate Board Member to assure that an acceptable effective date is designated.

The change notice is broken into Parts 1 and 2. Part 1 shows how to update the documentation. Part 2 is the special rework instructions required by Manufacturing or Field Service Operations on how to update a component or assembly that does not conform to the new revision.

(Note: The specific ECO form for this procedure is not included in this manual. However, several ECO forms follow. One of the example forms, Engineering Change Package (ECP), is simply an ECO cover sheet for a group of ECO's. An example of a filled-in group change is included. It includes the completed ECP cover sheet and two completed ECO forms. The other three completed ECO forms noted on the example ECP are not reprinted.)

<table>
<thead>
<tr>
<th>REQUEST FOR ENGINEERING ACTION</th>
<th>REA No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originator</td>
<td>Dept</td>
</tr>
<tr>
<td>Component, subassembly, or device:</td>
<td></td>
</tr>
<tr>
<td>Drawing(s)</td>
<td></td>
</tr>
<tr>
<td>Problem (in detail)</td>
<td></td>
</tr>
<tr>
<td>Solution recommended, if known</td>
<td>Date action required by</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td></td>
</tr>
<tr>
<td>Dept Manager approval</td>
<td>Date</td>
</tr>
<tr>
<td>Assigned to</td>
<td>Date forwarded for solution</td>
</tr>
</tbody>
</table>

1. QSR MANUAL
2. Sheet 8 of 8
3. Stock Room: What should be done with non-conforming purchased components in our stock room? By what date should the above action be complete?
4. Work-in-Process: What do we wish to do with the material on the floor?
5. Finished Goods: What do we do with the material in finished goods?
6. Field Service: What should be done to devices in the field?
7. Cost: Each department is responsible for reporting the cost of the change with respect to its area.

17. Effective Date: Each change shall be applicable to all units shipped after a particular date where the date is relatively unimportant because the change is a minor documentation change. In all other changes, an effective date must be assigned by the Board. If it is important to a particular functional area that a change be implemented by a date or not sooner than a date, it is the responsibility of the appropriate Board Member to assure that an acceptable effective date is designated.

The change notice is broken into Parts 1 and 2. Part 1 shows how to update the documentation. Part 2 is the special rework instructions required by Manufacturing or Field Service Operations on how to update a component or assembly that does not conform to the new revision.

(Note: The specific ECO form for this procedure is not included in this manual. However, several ECO forms follow. One of the example forms, Engineering Change Package (ECP), is simply an ECO cover sheet for a group of ECO's. An example of a filled-in group change is included. It includes the completed ECP cover sheet and two completed ECO forms. The other three completed ECO forms noted on the example ECP are not reprinted.)
## QSR MANUAL

### SOLUTION

<table>
<thead>
<tr>
<th>Charge No.</th>
<th>Priority</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>App. By</th>
<th>ECO Number</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes on back? YES  Sheets attached? YES

### PROCEDURE

1. Originator: Complete top of this form except for REA number.

2. Obtain your Department Manager's approval.

3. Forward original to Technical Services Manager who will assign the REA number.

Note: One copy will be returned to originator with REA number assigned.

If problem involves safety, effectiveness, or reliability, Technical Services will forward to the QA Manager a copy with the REA number assigned.

4. Technical Services takes appropriate action and also executes an ECO.

5. Technical Services returns a copy to Originator after resolution of problem.

### Form No. Rev. App. By Date

### COMPANY LOGO

<table>
<thead>
<tr>
<th>Engineering Change Order (ECO)</th>
<th>ECO #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Signatures | Date | Approvals | Date | Reason for Change |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Originator</td>
<td></td>
<td>Type A</td>
<td></td>
<td>[ ] Improve process [ ] Biocompatibility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[ ] Design improvement</td>
</tr>
<tr>
<td>Project Engr.</td>
<td></td>
<td>Type B</td>
<td></td>
<td>[ ] Correct error [ ] Cost reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[ ] Customer request</td>
</tr>
<tr>
<td>TYPE</td>
<td></td>
<td>Type C</td>
<td></td>
<td>[ ] Labeling or packaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[ ] Regulatory</td>
</tr>
</tbody>
</table>

### DESCRIPTION OF CHANGE

<table>
<thead>
<tr>
<th>Action</th>
<th>Drawings</th>
<th>REVISED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code</td>
<td>Affected</td>
<td>From To</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change action required</td>
<td>codes</td>
<td>Change action required</td>
</tr>
<tr>
<td>------------------------</td>
<td>-------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Purchasing and Production</td>
<td></td>
<td>Rework components in stock</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rework part in-process</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scrap in-process items</td>
</tr>
<tr>
<td>Make new parts</td>
<td>4</td>
<td>Other Action</td>
</tr>
<tr>
<td>Rework finished goods</td>
<td>5</td>
<td>Packaging Notify User of Part</td>
</tr>
<tr>
<td>Notify supplier</td>
<td>6</td>
<td>Employee training</td>
</tr>
<tr>
<td>See old parts for spares</td>
<td>7</td>
<td>510(k) required for Change</td>
</tr>
</tbody>
</table>
10. Purchasing and Acceptance Activities

INTRODUCTION
- Components
- Accessory Devices
- Contractors and Consultants

COMPONENT SELECTION AND VERIFICATION

PURCHASING AND RECEIVING OF PRODUCT
- Specifications
- Supplier Qualifications
- Acceptance Procedures
- Acceptance Criteria
- Testing and Inspection of Product
- Acceptance and Rejection Records
- Obsolete, Deteriorated, and Rejected Components
- Component Storage
- Component Traceability
- Written Test Procedures
- Sampling Plans
- Control Numbers

CONTRACTOR AND CONSULTANT ASSESSMENTS
- Interface Requirements
- Process Validation Requirements
- Device Servicing Requirements

CONTRACT STERILIZATION
- Labeling Requirements
- Quality System Requirements for Contract Sterilization
- Information Transfer
- Record Keeping
- Process Validation
- Bioindicators and Dosimeters
- Loading Configuration
- Preconditioning
INTRODUCTION

This chapter covers component specifications, supplier assessment, receiving components and the services rendered in manufacturing medical devices. Manufacturers of medical devices should maintain a consistent, systematic quality system which, along with other quality assurance activities, should assure that all components, materials, and services involved with the manufacture of medical devices are acceptable for their intended use. This control is a combination of: component and supplier selection and verification; data collection, analysis and corrective action; supplier, contractor, and consultant assessment; identification and status of product including labeling and/or quarantine; and operational procedures.

The establishment and maintenance of requirements, including quality requirements, is essential for the manufacturer when dealing with component suppliers, consultants, and contractors [820.50(a)]. The ability to meet specified requirements is important when evaluating the suppliers and service providers. Assessments of these providers shall be maintained and documented. Possible appropriate methods of accomplishing these goals include audits, checking with other clients, and previous performance data. If prior assessment is not possible, then the manufacturer should assess the service as it is being performed. Assessment shall be documented. Procedures for accepting incoming product shall also be established and maintained. Various acceptance activities may include inspections, tests, and other forms of verification. Acceptance or rejection of components and services shall be documented (820.80).

Components
"Component" is defined in 820.3(c) of the Quality System (QS) regulation as any material, substance, piece, part, software, firmware, labeling, or assembly, which is intended to be included in the finished, packaged, and labeled device. For example, fasteners, blood tubing assemblies and labels are components. This definition excludes "manufacturing materials," which by definition, are not intended to be included as part of the finished, packaged, and labeled device.

According to 820.3(p), "manufacturing material" is any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer. Examples of manufacturing materials include: cleaning agents, mold-release agents, lubricating oil, or other substance used to facilitate a manufacturing process which is not intended by the manufacturer to be included in the finished device.

Manufacturers of components sold only for further manufacturing of a medical device are not required to comply with the GMP requirements for finished devices. Many components of devices, such as transistors, containers, hardware, etc., are readily available in the marketplace and are not manufactured exclusively for use in devices. Many of these manufacturers supply only a small fraction of their production to finished device manufacturers. However, section 820.1 of the Quality System regulation encourages component manufacturers to use applicable GMP elements as guidance.

If a component is manufactured in the same or proximal facility, and produced for use in finished medical devices, then the component is considered part of the production of the finished devices and is subject to the applicable requirements of the GMP requirements. If the component is manufactured in a separate plant owned by the finished device manufacturer, then the manufacturer has flexibility in handling the quality assurance activities related to the control of components. One satisfactory approach is to have the plant that builds the components operate in full GMP compliance. Under this arrangement, the plant which does the final device assembly would still be responsible for ascertaining that the quality and integrity of incoming components have not been damaged during shipment. Alternately, the component manufacturing plant may not fully comply with Quality System regulation. Then the plant that does final assembly should handle the acceptance of these components with the same degree of control as if the components were purchased from an outside supplier.

For components such as labels, package inserts, packaging, etc., there is additional information in chapter 11, Labeling; and chapter 13, Packaging.

**Accessory Devices**

The Quality System regulation applies to manufacturers who produce finished accessories to devices intended to be used for health-related purposes. An accessory is any finished unit distributed separately but intended to be attached to or used in conjunction with another finished device. Therefore, any manufacturer of accessory devices should meet all FDA regulations for a finished device. These regulations include 21 CFR Part 807 Subpart E, Premarket Notification; 21 CFR Part 807 Subparts B,
Contractors and Consultants

Contractors and consultants generally provide a service rather than a physical component. This service should be treated in basically the same manner as physical components because these services affect the quality of the finished device. The combination of both services and physical components determines the quality of the finished device. Services should be obtained per 820.50, Purchasing Controls, and be controlled upon receipt using the applicable requirements in 820.30, Design Controls, 820.70, Production and Process Controls; 820.80, Receiving, In-Process, and Finished Device Acceptance, etc., depending on the nature of the service.

COMPONENT SELECTION AND VERIFICATION

Verification of physical components is a very important step toward producing a high quality product. Verification of components consists of determining through documented testing that a component will perform its function reliably in the intended application and under the most adverse environmental conditions in which the device is expected to be used. These conditions shall consider the needs of the user and patient [820.30(c)] and shall encompass the manufacturer's labeling claims for the device.

Components have to be carefully selected, using the requirements of the device as a guide. Components should be chosen so that they will not be over-stressed and will be compatible with the internal device environment, as well as the external environment that the device is expected to encounter during manufacture, distribution, and use. The components should then be appropriately tested, alone, and as part of the device, utilizing the specifications established for the component and the device. New components or components used in an unusual application will usually need extensive evaluation. This evaluation should include parameter and life testing as well as compatibility testing for both the internal and external environment. Well known industry standard components that are used in their normal application and that are not over-stressed will need only minor testing, which is usually an integral part of the verification of the device design. A record of any component verification testing should be maintained. This record should include the component identity and the testing methods that were used, as well as the actual test data and results.

PURCHASING AND RECEIVING OF PRODUCT

Component quality is maintained through correct specifications, procurement, incoming acceptance, storage, handling, installation, and change control. To monitor the adequacy of these activities and procedures, feedback from the quality system is needed. Corrections are made if necessary. In addition to maintaining quality, the manufacturer shall also establish and maintain procedures for identifying product during all manufacturing stages from receipt through installation (820.60 and 820.86). Product includes components, manufacturing materials, in-process devices, finished devices, and returned
devices.

Specifications

Component specifications are required as part of the device master record. Components are selected and their specifications are documented during the design of the device. The specifications should be well designed, achievable, and acceptable to suppliers. They should adequately describe the quality characteristics, dimensions, design, materials, performance, and any other features necessary to assure receipt of the item desired. For unusual, vital, new or key components the specification data is derived primarily from the verification data with minor details from the catalog data. For routine components, such as those that have been used for a long time or have a known performance history, a catalog designation may be adequate to describe a component and assure its purchase. For some components such as transistors, the catalog number also may be used to obtain complete specifications from a reference manual. Specifications should reflect both design requirements and quality/reliability needs. The quality level for each component should be specified. Components usually are available in several quality levels such as reagent grade, commercial grade, military grade, etc. In some cases, a significant increase in component quality can be obtained for a modest increase in cost by specifying a higher grade, thus reducing the probability of future quality problems and the possibility of significant associated costs.

Supplier Qualifications

A major factor in obtaining high quality components is the selection of suppliers. Although a manufacturer's knowledge of supplier operations may be limited and information about the operations difficult to obtain, the GMP requirement that a manufacturer is responsible for quality remains undiminished. To the maximum extent feasible, selection and qualification of suppliers by audits, performance analysis, etc., should be part of a quality system. If the manufacturer does not have the capability to test components for conformance to specifications, then supplier test data or outside lab results are acceptable provided that components are tested and inspected in a statistically valid manner to show their acceptability for use in the finished device. Any outside test results should be accompanied by relevant raw data used for the test so that judgments of authenticity may be made by the finished device manufacturer. Excluding a supplier whose components are unreliable from supplying components may help prevent problems with the final device and is certainly worthwhile as a cost reduction effort.

It is important to remember that raw components acquire cumulative value as they are processed through receiving, assembly, test, inspection, and as they ultimately become part of the finished device. If a component fails during assembly, or as part of the device, additional costs will be incurred for fault isolation, removal, replacement, inspection, testing, etc. When field failures occur, the ultimate cost of the component becomes even higher because its replacement requires travel, trouble-shooting, and retrofit. In addition, customer dissatisfaction, user injury, product liability action, medical device reporting, or regulatory action may result. Usually, the initial cost of a component is relatively
insignificant compared to the later cost should the component prove to be defective or improper for the selected use. Many recalls occur because manufacturers fail to qualify components properly or to assure that a supplier's manufacturing methods and quality system are adequate.

Acceptance Procedures

Written instructions are necessary to assure that components, manufacturing materials, etc. are properly identified, processed, and stored when received. Written inspection and test procedures are necessary to prescribe the:

- acceptance activities performed;
- dates acceptance activities are performed;
- the results;
- signature of the individual(s) conducting acceptance activities; and
- where appropriate, the equipment used.

Before acceptance, all components should be either physically separated (quarantined) or clearly identified as not yet accepted. The decision to separate or tag not-yet-accepted product should be made based on the characteristics of the device, the potential for mixups, plant conditions, and manufacturing practices.

Although 820.80 requires a written procedure for accepting components, the Quality System regulation in 820.5 allows discretion in the quality system. Thus a very small manufacturer, usually 10 or fewer employees, may only need very brief written acceptance procedures referencing the purchase orders and receiving tickets. As the size of the operation, the numbers of activities, and number of people involved increase, the need for comprehensive written instructions generally increases.

Acceptance Criteria

Manufacturers should have specific acceptance criteria for components. Acceptance criteria are the attributes of a component that determine its acceptability, such as appearance, dimension, purity, performance characteristics, etc. Typically, acceptance criteria are made a part of the inspection/test procedure. For example, if component specifications or a drawing adequately describe the attributes needed in order for the component to perform in its intended manner, these may be used as the acceptance criteria. If components or the suppliers of the components have a history of good performance, the components may be accepted for use after a visual check to assure they are the items intended and that they are not damaged or contaminated. Components, which need only a visual inspection, may be accepted using the purchase order data as acceptance criteria. The purchase order and/or receiving ticket should at a minimum contain the following information:

- name of supplier;
- description of the component or other product; and
For a standard component, the catalog number may be used as a description. QA personnel should determine whether the use of any "abbreviated" criteria are adequate during their audit of production rework, history records, complaint files, and service records.

**Testing and Inspection of Product**

The minimum acceptance activity per current practice requires that all incoming components and other product receive at least a visual inspection for contamination and/or damage and be identified as the component specified on the purchase order. A manufacturer accepting the product has the discretion to determine when and where product should be inspected, sampled, and tested for conformance to specifications depending upon the risk that failure of that component may pose. As appropriate, product may be tested and/or inspected by:

- the supplier;
- when received;
- during manufacture of the device; or
- as part of the finished device.

If components are tested as part of the finished device, the testing should be able to reveal failed and "out-of-spec" components and not just that the finished device does not meet specifications. This determination, of course, may be performed after removing the component from the device. The rejection shall be documented [820.80(b)].

Manufacturers who decide not to sample or test specific components should be able to justify that decision based on such factors as knowledge of the supplier's previous performance in providing high quality components, the component performance history, and application of the components in the device. Manufacturers may rely on component suppliers to conduct testing if the manufacturer specifies or is knowledgeable about the supplier's quality system, particularly the inspection and test programs and the supplier has specifications that properly define the manufacturer's acceptable limits for the component or material parameters. These specifications may be used to meet the device master record requirements for component specifications, if these accurately reflect the parameters, composition, and configuration required for the component to perform the function for which it was selected. Supplier specifications are usually adequate for standard components. However, a manufacturer who relies on supplier specifications usually has no control over changes in these and, therefore, should assure at an appropriate point in the manufacturing process that the components received meet the desired specifications.

If components are tested by the supplier, acceptance of components can be based on certification and review of test data submitted by the supplier for the specific components provided. Certification should accompany each lot of components. When certification is used, the manufacturer should periodically
verify the validity of the certification through an assessment of the supplier.

Where historical data shows that certain components or other product have been substandard and resulted in a device failing to meet specifications, or where performance history has not been established, specific steps should be taken to assure components meet specifications. Typically, this task is accomplished by sampling and testing each lot of components to assure that the components meet specifications. Where appropriate, all significant or high risk components should be sampled and tested.

Manufacturers may test entire assemblies of components rather than individual components. If, however, testing an assembly cannot assure fitness-for-use of the components, then components should be tested on an individual or lot basis, whichever is appropriate. For example, assemblies with an internal feedback circuit could have a very marginal component. Because of the circuit design, the condition of the marginal component might not be detected by testing the entire assembly. Therefore, the feedback loop in the assembly should be opened during one of the tests, or the individual components should be tested.

When using a contract laboratory to test production components, the laboratory becomes an extension of the device manufacturer's quality system. The device manufacturer is responsible for assuring that the contractor's test and inspection procedures are acceptable. This assurance maybe obtained by audits of the laboratory, by the lab staff, and by the finished device manufacturer.

Inspection and testing will not improve the quality of components or other product; however, if the inspection and testing is appropriate and performed adequately, these activities can be used to prevent or significantly reduce the use of low-quality or defective product. Through feedback into the overall quality system, data on products will help identify basic causes of problems and lead to solutions (820.100). If problems are found, actions such as design changes, tighter acceptance criteria, supplier assessments, or change of suppliers may be appropriate.

Acceptance and Rejection Records

Adequate records shall be maintained to provide objective evidence that components were inspected and accepted, or rejected. These records are a part of the device history record and should be maintained in a format that facilitates review. The records, however, are not required to be maintained in a single file with other production history records, and are typically filed in the receiving or quality control area according to part number or component nomenclature. Small manufacturers may use purchase orders or packing slips to record acceptance and rejection if they contain adequate information.

The Quality System regulation specifies in 820.80(b) that a record of component acceptance and rejection be maintained. Typically, acceptance/rejection records should contain:

- acceptance or rejection documentation;
- number and type of deficiencies;
● quantity approved;
● quantity rejected; and
● nature of corrective action taken.

Obsolete, Deteriorated, and Rejected Components

Obsolete, deteriorated and rejected components shall be identified (820.60, 820.86, and 820.150) as such and be placed in a separate quarantine area or specially identified area to prevent mixups. If practical, components should be individually identified as rejects. Where it is not feasible to tag each rejected component, as in the case of transistors, bolts, bottles, etc., containers or packages of rejected lots should be clearly marked and otherwise appropriately segregated from accepted components. See 820.86 for clarification. Manufacturers should determine the need for a separate written procedure for handling these components based on the size of the manufacturer and complexity of their devices and operations. Disposition of nonconforming product shall be documented [820.90(b)].

Records for rejected components should state whether the components were returned, scraped, reworked, etc. In very small manufacturers, disposition can be recorded directly onto the purchase order, receiving ticket, or other associated document. Small-to-medium sized manufacturers generally record disposition on the form used to receive components. Most large manufacturers record disposition of rejected components on standard forms such as a Nonconforming Material Report (NMR).

When components, materials, etc., become obsolete, many manufacturers assign new identification numbers to the new version of these components etc. The obsolete items are retained for other uses, such as repair parts, engineering projects, etc. In these cases, the old and new items should be adequately segregated and/or identified to prevent inadvertent use of obsolete components in production.

Component Storage

Each manufacturer shall establish and maintain procedures for control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, its condition shall be assessed as appropriate. 820.150 procedures shall be established and maintained that describe methods for authorizing receipt from, and dispatch to, storage areas and stock rooms.

Although not a direct requirement, all raw materials and components used in the finished device should be received through a central control point. Centralized receiving leads to orderly storage, limits access to stored material, and aids a manufacturer in meeting other GMP requirements. Components and other product should be identified or stored so that it is obvious at all times that product has been accepted, rejected, or is awaiting a disposition decision. A quarantine area can be either a physically secure area or simply limited access area identified as a quarantine area. If special environmental storage conditions are
required such as for many biologically derived components, these conditions should be controlled and monitored and the associated specifications included in the device master record.

When the device is to be sterilized, storage conditions should be selected, as appropriate, to prevent contamination of components and packaging by bacteria or filth. Also, temperatures should be controlled as necessary to prevent or reduce the growth of bacteria. The higher bioburden (bacteria, etc.) levels may challenge the sterilization cycle to an extent greater than the capability established during process validation and, thereby, result in a sterility assurance level that may not meet the finished device specification. Some components, particularly those used in the manufacture of in vitro diagnostic devices, if not stored properly, may support growth of bacteria.

**Component Traceability**

The criteria as stated in 820.65 for determining the need to have traceability via a unit, lot, or batch control number of a device specifies devices intended for surgical implant into the body or those that support or sustain life and whose failure to perform, when properly used in accordance with instructions for use provided in the labeling, can be reasonably expected to result in a significant injury to the user. Identification of traceable devices should be based on the health hazard presented if a device fails to meet its performance specifications when operated as intended. Because of the design control requirements (820.30), user error and the environment are not considered by FDA as a means for excusing the lack of device performance. User error is not a performance failure, although it could be considered a result of inadequate directions for use, other inadequate labeling, or poor human factors design. The environment could result in failure of a device but it should not effect the result of the device failure.

FDA is concerned about the failure of components that would result in sudden or catastrophic device failure, which can reasonably be expected to result in significant injury to the user, such as:

- no output from an implantable cardiac pacemaker;
- fracture of an implanted orthopedic implant;
- runaway in an implanted cardiac pacemaker;
- misfiring of a synchronized defibrillator; etc.

A manufacturer should know in detail how the device functions and the purpose of each component in the finished device. If as a result of a failure, the performance, lack of performance, or effect on safety or effectiveness of the finished device could result in significant injury to the user when the device is properly used in accordance with instructions in the labeling, the component under consideration may require increased control and traceability. The effect that each component will have on finished device performance, should the component fail to perform as intended, should be determined. Thus, manufacturers should carefully study the possible failure modes of their devices and decide which components are truly critical under the various modes. This determination may be time-consuming with respect to some devices, but it is necessary. It will, in the long run, save manufacturers liability, repair,
and replacement costs. To make such a determination, manufacturers should conduct reliability tests and failure effects analyses during the design phase in order to accurately identify critical components.

The number of components that need to be considered as potentially needing to be handled as traceable components can be reduced by considering the reliability of components and whether they "reasonably" can be expected to fail. For example, power cords, clamps, plugs, etc. seldom fail. Therefore, manufacturers may not need to consider extensive tracing requirement of these components. Also, manufacturers can consider a subassembly as a component and, thereby, reduce the number of identification and record keeping activities, but all rationale and justification should be documented.

**Written Test Procedures**

A device manufacturer shall establish and maintain procedures to ensure that all purchased and otherwise received product conforms to specified requirements (820.50) and establish and maintain procedures for acceptance activities [820.80(a)]. The manufacturer shall assure that all lots of components or other products are accepted, sampled, tested and/or inspected using written procedures. The inspection/test procedure for each component shall be correct [820.30(d), Design Output and 820.30 (h) Design Transfer], dated, and approved. The design verification procedures usually may be used to develop production test procedures. The procedure should specify, as appropriate,:  

- items to which it applies,  
- product characteristics to be inspected/tested,  
- acceptance/rejection criteria,  
- test method(s),  
- data forms,  
- sampling plans, and  
- necessary test inspection equipment and tools.

**Sampling Plans**

When assuring that components and other products meet acceptance criteria, manufacturers may test either all components or may test a portion of the components using a sampling plan based upon an acceptable statistical rationale (820.250). A manufacturer shall be prepared to demonstrate the statistical rationale for any sampling plan used. Plans should be developed by qualified mathematicians or statisticians, or be taken from established standards such as ANSI Z1.4. It should be recognized that all sampling plans have a built-in risk of accepting a bad lot.

This sampling risk is typically determined in quantitative terms by deriving the "operating characteristic curve" for the selected plan. Each sampling plan has a characteristic curve. ANSI Z1.4 contains operating characteristic curves for sampling plans presented in the standards, and it can be used to determine the risk a sampling plan presents. A manufacturer should be aware of the risks the chosen plan presents. Operating characteristic curves are a means of graphically showing the relationship
between the:

- quality of lots submitted for sampling inspection, usually expressed in percent defective, but may be expressed in defect per hundred units; and
- the probability that the sampling plan will yield a decision to accept the lot, described as the "probability of acceptance."

**Control Numbers**

Manufacturers of surgically implantable or life sustaining devices whose failure to perform when properly used can be reasonable expected to result in a significant injury shall establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and when appropriate components. Control numbers should be assigned to each unit, lot or batch of components that were manufactured under similar conditions over the same time period so that defects can be traced to the component manufacturer and the cause of the defects determined and corrected. If a subassembly is regarded as a traceable component by the manufacturer, a control number for that traceable subassembly shall be recorded in the device history record.

**CONTRACTOR AND CONSULTANT ASSESSMENTS**

Manufacturers shall establish and maintain the requirements, including quality requirements, that will be met by contractors/consultants that perform a service for them. To aid in accomplishing this task each manufacturer shall:

- evaluate and select contractors/consultants based on their ability to meet specified requirements, including quality requirements. This evaluation shall be documented.
- define the type and extent of control to be exercised over the contractors/consultants based on the evaluation results.
- establish and maintain records of acceptable contractors/consultants.

Contractors and consultants often provide information or a service rather than a physical component. However, the thought and control processes are similar whether one is working with services or with physical product. The input from contractors and consultants have a definite impact on the finished device. Services may include: design activities, various product verification/validation activities, sterilization, routine maintenance, and calibration of equipment.

Each manufacturer shall provide adequate resources and trained personnel to properly assess the activities of their contractors and make adjustments as necessary. Contractors and consultants maybe assessed based on their applicable education, experience, ability, resources such as facilities and
equipment, list of clients, patents, technical reports, etc. Assessment may include conducting internal quality audits [820.20(b)(2)]. Therefore, each manufacturer that is having important work done by a contractor should inform the contractor that their quality system and activities may be audited. These services may include janitorial, consultants, design work, calibration, sterilization, laboratory, and maintenance.

Interface Requirements

At various stages of product development the manufacturer may need to interface with different groups. If a need for this interface relationship arises during the design phase, a plan shall be developed describing the interface with different groups or activities during the design process [820.30(b)]. By planning for outside services, and including these providers in selected design review meetings, a manufacturer increases the probability of receiving a service that meets requirements. Also the manufacturer is held responsible for work done by outside contractors or consultants. Thus, it is in the manufacturer's best interest to keep providers adequately informed and to monitor contractors to ensure that the correct design, production, or process controls are applied to contractor services to ensure the service or finished product conforms to its specifications (820.30, 820.50, 820.70, and 820.80).

Process Validation Requirements

Regardless of whether a manufacturer or a contractor performs the actual work, the manufacturer is responsible for establishing and maintaining control of the process parameters for the validated process (820.75). Established procedures for validation and the validation results should offer a high degree of assurance that the process consistently produces an output that meets pre-established specifications. Validated processes shall be performed by a qualified person(s) and be documented regardless of whether the manufacturer or an outside contractor performs the validation activities. For more information see Process Validation, chapter 4.

Device Servicing Requirements

If a manufacturer contracts for device service with another party, the assessment and selection of such contractors shall be done according to 820.50 Purchasing Controls. Such service activities and reports should be periodically reviewed to assure that the service activities meet GMP servicing requirements as briefly described below.

Device servicing performed by contractors and/or consultants shall be conducted using established procedures for performing and verifying that the service meets specified requirements (820.50 and 820.200). A written report on the servicing shall include:

1. the name of the medical device serviced;

2. any device identification(s) and control number(s) used;
3. the date of service;
4. the individual(s) servicing the device;
5. the service performed; and
6. the test and inspection data.

Each manufacturer should analyze the service reports they receive directly, as well as the ones they receive from contractors, using the appropriate statistical methodology referenced in 820.100. It is important that this service data be collected and organized such that it can be analyzed to determine if quality problems exist. See Chapter 15, Complaints, for more details. If the report represents an event which is reportable to FDA under medical device reporting (MDR) requirements in 21 CFR part 803 or 804, these reports shall be handled as complaints using 820.198.

Contract agreements between the manufacturer and contractors and/or consultants will vary in their degree of complexity. The most comprehensive is probably the agreement between the manufacturer and the contract sterilizer. Thus, the contract sterilization agreement is an excellent example of what is involved in setting up a contract between the device manufacturer and a contractor. The steps necessary for an agreement may be less extensive with other contracts than it is with the sterilization contract; however, the sterilization contract does provide a good basis for understanding this contractual agreement.

**CONTRACT STERILIZATION**

Manufacturers of medical devices frequently use contract sterilizers to provide sterilization processing for their devices prior to distribution. Contract sterilization of medical devices shall be performed so that the device manufacturer and the contract sterilizer meet the applicable parts of both the QS regulation and the labeling requirements of 21 CFR 801.

**Labeling Requirements**

Manufacturers of sterile devices commonly label devices as sterile at one establishment and ship them to another facility or to a contract sterilizer for sterilization. Shipments of nonsterile devices labeled as sterile are clearly misbranded and adulterated, and they may be diverted into consumer channels, thus creating a health hazard. FDA recognizes that this longstanding practice is an economic necessity for many manufacturers. Therefore, to meet the needs of these manufacturers in a way that will also assure the protection of the public health, FDA added Part 801.150(e) to the Code of Federal Regulations (CFR). This part identifies the necessary markings for such shipments and requires a written agreement which specifies the sterilization process. Part 801.150(e) It is reprinted below:
(e) As it is a common industry practice to manufacture and/or assemble, package, and fully label a device as sterile at one establishment and then ship such device in interstate commerce to another establishment or to a contract sterilizer for sterilization, the Food and Drug Administration will initiate no regulatory action against the device as misbranded or adulterated when the nonsterile device is labeled sterile, provided all the following conditions are met:

(1) There is in effect a written agreement which:

(i) Contains the names and post office addresses of the manufacturers involved and is signed by the person authorizing such shipment and the operator or person in charge of the establishment receiving the devices for sterilization.

(ii) Provides instructions for maintaining proper records or otherwise accounting for the number of units in each shipment to insure that the number of units shipped is the same as the number received and sterilized.

(iii) Acknowledges that the device is nonsterile and is being shipped for further processing, and

(iv) States in detail the sterilization process, the gaseous mixture or other media, the equipment, and the testing method or quality controls to be used by the contract sterilizer to assure that the device will be brought into full compliance with the Federal Food, Drug and Cosmetic Act.

(2) Each pallet, carton, or other designated unit is conspicuously marked to show its nonsterile nature when it is introduced into and is moving in interstate commerce, and while it is being held prior to sterilization. Following sterilization, and until such time as it is established that the device is sterile and can be released from quarantine, each pallet, carton, or other designated unit is conspicuously marked to show that it has not been released from quarantine, e.g., "sterilized awaiting test results" or an equivalent designation.

Quality System Requirements for Contract Sterilization

The sterilization process are performed in compliance with applicable parts of the Quality System regulation for medical devices because sterilization is a manufacturing process. Thus, the contract sterilizer is a manufacturer [(820.3(o)] and the device master record (DMR) shall contain, or refer to, the location of sterilization process specifications. Process specifications may be generated by either the manufacturer, contract sterilizer, or by both parties, although overall responsibility rests with the finished device manufacturer. The device manufacturer is ultimately responsible for assuring that its devices are sterile. The responsibility for specific tasks may be delegated to a contract sterilizer, but the device manufacturer retains the ultimate responsibility. The contract sterilizer is subject to those parts of the QS regulations that apply to the operations that it performs for the finished device manufacturers, e.g., equipment maintenance and calibration, in-process controls, and associated record keeping, etc. Thus, both the manufacturer and the contract sterilizer share the responsibility to comply with the QS
Because the responsibility for effective sterilization is shared between the device manufacturer and the contract sterilizer, it is essential that the two parties clearly define in writing the division of responsibility for every aspect of the sterilization process. The QS arrangements between the manufacturer and the contract sterilizer may be in the same written agreement used to cover the 801.150 (e) labeling requirements. It is the manufacturer's and contractor's responsibility to assure the agreement is a workable practical document and is followed by both parties. FDA inspects finished device manufacturers and contract sterilizers to determine compliance. The following is QS related information that should be in the written agreement for contract sterilization and implemented during production, sterilization, and release.

**Information Transfer**

The manufacturer and contract sterilizer should designate the individual(s) at each facility responsible for coordinating the flow of information between establishments and for approving changes in procedures. All technical, procedural, and other information that pertains to the sterilization process and associated activities should pass through these designees. The manufacturer and the contractor shall agree to inform one another of any device or process changes, especially those that may require cycle requalification.

**Record Keeping**

Documentation such as device master record procedures, device history records, etc., to be used and maintained should be specified. If changes are made to the documentation, both parties should agree on the manner in which the changes are to be made. These documentation changes shall comply with QS requirements in 820.70(b) and .75(c) for manufacturing and process specification changes, and with 820.40(b) for changes in device master records.

**Process Validation**

The device manufacturer has primary responsibility for the validation of the process used to sterilize its devices. Commonly, responsibility for portions of the validation study are delegated to the contract sterilizer in the written agreement. The manufacturer should work with the contract sterilizer to assure that the facilities, equipment and processing parameters (including preconditioning and aeration steps) will provide for effective sterilization and will not adversely affect the devices or their packaging. Validation is required for every device or device family. The written agreement should identify responsibility for all aspects of validation and define the criteria, frequency, and responsibility for requalification. Likewise, the agreement should identify the documentation that is maintained for validation studies.

**Bioindicators and Dosimeters**
The agreement should specify responsibility for placement, retrieval, handling, and processing of product samples and any biological, chemical, or physical indicators. The agreement should include instructions for packaging and shipment of indicators and samples to test laboratories for analysis.

**Loading Configuration**

The loading parameters for each lot of device(s) or device family should be specified. The routine product load configuration should conform to the validated load configuration. It is not recommended that a contract sterilizer mix products from different manufacturers in processing cycles unless validation studies have proven the effectiveness of the cycle for those mixes or worst case mixes, and the customers are informed about the practice.

**Preconditioning**

The agreement should address preconditioning requirements for external preconditioning and/or in-chamber conditioning if required by the sterilization process.

**Cycle Parameters and Process Control**

The written agreement should specify the cycle parameters to be achieved during processing. After the process is qualified, the contract sterilizer is responsible for maintaining control over the process to make certain that process specifications are routinely achieved. Cycle parameters should be clearly defined in written specifications, accurately monitored, and the actual parameter values achieved during each run should be recorded.

The primary manufacturer should produce the product under a quality system, which includes appropriate environmental control procedures such as bioburden control. Thus, the product is the "same" product as that for which the original process was developed or specified.

**Post-sterilization Handling and Aeration**

The agreement should address procedures for post-sterilization quarantine of the product before release for distribution. While waiting for release, the pallets, cartons, or designated unit shall be marked to indicate the status of the product; for example, "sterilized: awaiting test results," or an equivalent statement. If an aeration period is required, it should be specified. Both parties should acknowledge that the product is not to be shipped for commercial distribution until it is properly approved for distribution in accordance with procedures in the agreement.

If correctly labeled, a device that has been sterilized may be shipped to a **controlled** distribution point before final release by the manufacturer. Routine distributors are **NOT** considered to be "controlled distribution points." Shipments to a company warehouse or to another finished device manufacturer may
be acceptable as long as the manufacturers are able to show that they have control of the product until final release and could recall it if necessary. See CFR 801 Subparts A & E and QS sections 820.160, Distribution, and 820.80(d), Final Acceptance Activities.

**History Records and Review**

Both the manufacturer and contractor should agree on the procedures and responsibility for reviewing and approving the device history records.

**Finished Device Release**

The agreement should include device release procedures. Individuals responsible for approving device release for distribution should be identified. A contract sterilizer may handle the final release of a batch of sterilized devices. The manufacturer should make sure, however, that this agreement is part of a written contract. In addition, the manufacturer should: audit or have a consultant audit the contract sterilizer; review the contractor's own QA audit report; or obtain written certification of compliance to assure that personnel and procedures are adequate to meet the requirements of 820.160, Distribution, and, 820.80(d), Final Acceptance Activities.

**Audits of Both Facilities**

The device manufacturer should audit his quality system and assure by audits or other means such as a review of the contractor's own QA audit that the contractor has adequate control over the sterilization process. The agreement should cover the extent and frequency of the audit, corrective actions, records, confidentiality, and the auditor(s).

**Training**

The manufacturer should assure that the entire sterilization process is performed and controlled by properly trained operators. The agreement should provide the manufacturer access to applicable training records during agreed upon audits.

**Nonconformance**

Both parties should mutually agree to inform one another if the device or process deviates from the agreed upon specifications. As appropriate, the nonconformance should be investigated, evaluated, and, if necessary, corrective actions should be instituted. The parties should consider and agree on conditions requiring corrective action and document all reprocessing. The agreement should specify the individuals that should be contracted regarding any changes or deviations in the manufacturing or sterilization process. It should also specify the individual at the manufacturer that should be contacted when product is damaged to determine how the product should be handled at the contract sterilizer.
It is highly recommended that manufacturers of sterile medical devices read Sterile Medical Devices-A GMP Workshop Manual. This publication may be obtained from National Technical Information Services (NTIS), phone: 703-487-4650. The ordering number is: PB84188713. As of 7/96 the price is $71.50 for a paper copy and $12.50 for a microfiche copy.

FINISHED DEVICE EVALUATION

Finished device inspection is typically a final test and review of safety, performance, labeling, appearance, and configuration characteristics to assure the device meets the acceptance criteria established in the DMR. For many medical devices this assurance requires an analysis, electrical test, mechanical test, or other technical tests. For some simple devices, however, such as eyeglass frames, a visual or dimensional check may be sufficient to prove acceptability. For both simple and complex devices the manufacturer shall have written specifications or criteria for determining the acceptability of the finished device. It is important that the device characteristics to be evaluated are defined and also, where applicable, the equipment, environment, and handling procedure should be defined and established.

Sampling Plans

To show the manufacturing process is operating in a state-of-control, the process may need to be validated as explained in chapter 4, Process Validation. Testing product by using a sampling plan based upon an acceptable statistical rationale may demonstrate that the process continues to operate in a state of control. A manufacturer should be prepared to demonstrate the statistical rationale for any sampling plan used. Plans should be developed by qualified mathematicians or be selected from established standards such as ANSI Z1.4. Copies of this standard may be obtained by writing to: American National Standards Institute, 11 West 42nd Street, 13th Floor, New York City, NY 10036, or phone 212-642-4900.

All sampling plans have a built-in sampling risk of shipping devices that do not meet product specifications. Each sampling plan can be graphically illustrated to show the relationship between: the quality of lots submitted for sampling inspection and the probability that the sampling plan will yield a decision to ship the lot. ANSI Z1.4 contains operating characteristic curves for sampling plans presented in them. These curves can be used to determine the risk each sampling plan presents.

When sampling plans are used, there exists the possibility that a few defective devices will be shipped to the user. Thus, manufacturers should be aware of the risks a particular plan presents to the manufacturer and to the user. Questions such as those listed below should be considered before selecting a sampling plan.

- Will the defect be obvious to the user? If not, what are the consequences of using the defective device?
What is the state-of-the-art technology for 100% valid testing of this device?

Is the testing destructive?

Does the competition use sampling?

What is the probability of a product liability suit?

What are the regulatory consequences?

Does the marketplace expect or accept devices that have been sample tested and/or inspected?

Manufacturers should recognize that straightforward logical answers to these questions may not always be suitable. Acceptance status for devices may be influenced by the price the user is willing to pay -- 100 percent testing usually costs more than sampling. Destructive testing makes 100 percent testing impossible. Whether sample testing and inspection of a particular family of devices is acceptable to the user also changes with technology. Where 100% valid automatic testing is not feasible, validation of the process and the product with a follow up sampling plan is usually the preferred method of establishing and maintaining a quality system, which can continuously produce a device that meets specifications.

Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework, to ensure that it meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the device history record (DHR) [820.90(b)(2)].

When a device fails testing, it should not be repeatedly retested until it passes. The problem should be corrected. If a manufacturer's acceptance procedures allow acceptance after repeated testing and rework, there should be a valid basis for such an acceptance procedure. Failed devices shall be identified and segregated from acceptable devices and from the flow of the production process.

Labeling and Packaging Inspection

The manufacturer shall establish and maintain procedures to control labeling. This control includes the label's integrity, inspection, storage, control numbers, and labeling related operations (820.120).

The manufacturer shall control labeling and packaging operations to prevent labeling mixups. The label and labeling used for each production unit, lot, or batch shall be documented in the DHR [820.120(d)]. Where a control number is required by 820.65, that control number shall be on, or shall accompany, the device through distribution [820.120(e)]. The DHR shall include or refer to the location of the primary identification label and labeling used for each production unit [820.184(e)].
The manufacturer shall ensure that the device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution (820.130, Device Packaging). This may include containers and packaging examination as applicable to assure they are not damaged or misbranded. All devices shall have the correct labels, package inserts, and/or manuals as specified in the DMR.

**Records**

A DHR is a compilation of records containing the production history of a finished device [820.3(i)]. However, procedures for establishing and maintaining DHR shall be developed. These records demonstrate the device is manufactured in accordance with the DMR. The DHR shall include or note the location [820.80(e), 820.184] of:

- dates of manufacture;
- quantity manufactured;
- quantity released for distribution;
- acceptance records demonstrating the device is manufactured in accordance with the DMR;
  - date of acceptance
  - results of acceptance activities
  - signature of person(s) performing acceptance activities
  - where appropriate, equipment used
- primary identification label and labeling used for each production unit; and
- any device identification(s) and control number(s) used.

The DHR should be reviewed before distribution because these records are used to show that finished devices are manufactured in accordance with, and meet, the specifications in the DMR.

Beside these requirements, some device manufacturers should fulfill an additional traceability requirement if their device is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with the label instructions for use can be reasonably expected to result in a significant injury to the user. For these devices procedures shall be established and maintained to identify a control number for each unit, lot, or batch of finished devices and, where appropriate, components. The control number is used to trace a defective lot and facilitate corrective action. Identification of devices shall be documented in the DHR (820.65).

**Product Release**
Finished device manufacturers shall have sufficient controls to assure that only devices that have passed test and inspection are released as discussed in chapter 14, Storage, Distribution and Installation. The manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mixups (820.60). Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. To prevent mixups, not-yet-accepted and rejected devices shall be controlled to prevent mix up with devices that have been through final evaluation and accepted for release [820.80(d)]. Methods of controlling non-releasable product include storage location, boxing, or manifest tagging. The desired end result is to assure operations are in a state-of-control. Finished devices should not be released for distribution until:

- the activities required in the manufacturers DMR are completed;
- the associated data and documentation are reviewed;
- the release is authorized by the signature of a designated individual(s); and
- the authorization is dated.

**EXHIBITS**

Examples of forms that may be used for purchasing, accepting, receiving, and inspecting components are exhibited at the end of this chapter. These examples show the types of information required by the Quality System regulation. Procedures and forms for a particular situation may be more or less comprehensive than these, and may assume other formats or arrangements according to need.

**Purchase of Components**

This exhibit is a specification for purchasing a zener diode and is typical of device master record documents that are used to purchase components. This spec describes the diode in sufficient detail for the correct part to be procured.

**Acceptance of Components**

This example is intended as an acceptance procedure that may be followed by a small to medium size manufacturer. The procedure has space for the number, revision level, and a blank for "ECN History." The history blank is for adding brief notes about changes that have been made to this procedure. Included as part of this procedure is a "Receiving History Log" which immediately follows the procedure. The other forms mentioned in the procedure are not reprinted; however, similar forms are included with the "Procedure for Receiving and Inspection of Material" described below with the example located immediately following the "Receiving History Log."

**Material Receiving and Inspection Procedure**
This document is a more extensive receiving procedure than the one discussed above and it can be used by a medium to large manufacturer. As part of this procedure you will note an extensive revision record section. Also, part of the procedure is a flow chart which outlines the steps in the procedure and the branches for each step. Next is a "Daily Report of Goods Received" which includes the supplier name, quantity received, lot number or item number, purchase order or requisition number, and information on where the item was sent. The next item in the procedure is a "Receiving and Inspection Report" which contains information about the item and the sampling and testing performed on the item. The report includes an acceptance or rejection slot along with a space for the cause for rejection. The procedure continues with a "Daily Inspection Log" which is a summary of the items received and their disposition, either accepted or rejected. Finally, as part of the procedure, we find examples of the decals to be used to accept, reject, or quarantine the incoming items.

Identification Decals and Forms

Examples of decals and travelers used to identify materials, components and in-process assemblies are exhibited. Two of the decals deal with components and can be used as a means of assuring proper disposition of these items. A "Material Lot Identification" is exhibited which is used to identify components in a container. This form has space for, among other information, lot number, expiration date, quantity in the subject container, date it was issued to stock, and the person who received the container. The final example in this group is a "Stock Requisition" form, used whenever items are being released from stock to production. This form contains information such as, part number, quantity ordered and issued, and lot number. Note that part of this form is used to indicate if the issued item is to replace a defective item.

Receiving Rejection Notice

This form is used when incoming components and materials are rejected and includes sections for the inspector's report listing the sampling plan, specification tested for, number of defects, and a description of the defects. There is a section for a preliminary review, if necessary, and finally a section for the Material Review Board (MRB) decision on the disposition of the rejected lot. A MRB may accept temporary deviations that do not affect safety and effectiveness. These deviations or changes should be approved by the MRB or other designee. MRB activities should be performed per a written procedure and otherwise meet GMP requirements. The MRB should not change a device master record (DMR) drawing or be used as a substitute for the primary change control system of a manufacturer.

Sheet 1 of 1

TITLE: IN4278 ZENER DIODE SPECIFICATION NUMBER

Drafted by App. Date

REV. ECN History Date
1. SCOPE: This specification describes a one-watt zener diode used for voltage reference in the XYZ Stimulator.

2. ELECTRONIC CHARACTERISTICS

2.1 Zener Voltage: 3.1 vdc @ 76 madc

2.2 Maximum Zener Impedance: 10 ohms @ 76 madc

2.3 Reverse Leakage Current: (25%) 100 microamps (max) @ 1 vdc

3. TESTING: All diodes shall meet the requirements of JANTX IN4278 as specified in MIL-S-19500/127G.

4. PHYSICAL CHARACTERISTICS

4.1 Diodes shall be packaged in a void-free silicone case.

4.2 Leads shall be readily solder able.

5. MARKING

5.1 The cathode shall be identified by a color band.

5.2 An identification number and lot number or date code shall represent a specific manufacturing period.

5.3 All markings shall be permanent such that cleaning solutions will not remove the markings.

6. CERTIFICATION

6.1 A certification of compliance with this specification and a test data sheet must accompany each lot shipped.

6.2 Certification must include a statement that no changes have been made in materials or physical or electrical characteristics.

7. APPROVED SUPPLIERS

7.1 XXXXXXXXXXXXXXXXXXXXXX
TITLE: ACCEPTANCE OF COMPONENTS Sheet 1 of 3

1.0 SCOPE

These procedures are to be followed in the receipt, inspection, and storage of product such as raw materials, components, parts, manufacturing materials, etc., used in the manufacture of the XYZ Stimulator, a device that does not require traceability per 820.65.

2.0 RECEIVING

2.1 All incoming shipments must be examined for external signs of damage. If the shipment is damaged, immediately notify Purchasing and move the shipment to the unloading Hold area until disposition is decided by Purchasing.

2.2 Upon receipt, check each shipment against the corresponding purchase order and verify identity and quantity. The purchase order may include, reference, or have attached purchase specifications.

2.3 Enter the appropriate data into the Received Goods Log for each shipment received.

2.4 After completing the data entry, attach a yellow "HOLD" tag to the product and immediately move the products to the receiving quarantine area. The pink copy of the purchase order must accompany the product.

2.5 Notify Quality Control when materials requiring inspection are received in the quarantine area. This information is obtained from the device master record specification for the item ordered.

2.6 Quality control shall, after examining the product for damage and identity, move the product, etc., to be inspected to the Receiving Inspection area.
3.0 INSPECTION

3.1 Pull the inspection history file for the product to be inspected. This file contains the Receiving History form and inspection procedure. Enter the appropriate data from the purchase order onto the Receiving History form and perform the inspection per the procedure.

3.2 The QC manager shall assign a five digit lot number to each supplier lot received and enter the number on the Receiving History form.

3.3 After the inspection is completed, enter on the Receiving History form:
   a. the quantity accepted and sent to stock;
   b. the quantity rejected; and
   c. your signature and the date.

4.0 DISPOSITION

4.1 Receiving and test data for each shipment are sent to the designated individual for review and the decision regarding the acceptability of the lot.

4.2 For accepted product, enter the quantity accepted, date accepted, and lot number on a green "ACCEPTED" tag, attach the tag to the product, etc., and move it the stockroom.

4.3 For rejected product attach a red "REJECTED" tag to the rejected product and complete a Rejected Material form. Place all rejected product in the rejected quarantine area and forward the Rejected Material form to Quality Engineering for disposition.

5.0 STOCKROOM

5.1 All items entering the stockroom must be accompanied by a green "ACCEPTED" tag.

5.2 Components and other materials shall be stored and issued per SOP 17320.

5.3 Components and other materials will be issued from the stockroom on a first-in, first-out basis. All materials with a limited shelf life or requiring controlled storage conditions will be stored appropriately.
per SOP 17321.

Note: Sheet 3 is the Receiving History log for this procedure. The other forms mentioned in this procedure are not reprinted. However, similar forms are included with another procedure located later in this chapter.

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purchase</td>
</tr>
<tr>
<td>Order #</td>
</tr>
<tr>
<td>Lot #</td>
</tr>
<tr>
<td>Date Rec'd</td>
</tr>
<tr>
<td>Supplier</td>
</tr>
<tr>
<td>Lot Size</td>
</tr>
<tr>
<td>Quantity Accepted</td>
</tr>
<tr>
<td>Quantity Rejected</td>
</tr>
<tr>
<td>Inspect Date</td>
</tr>
<tr>
<td>Comments</td>
</tr>
</tbody>
</table>

Sheet 3 of 3

RECEIVING HISTORY RECORD
PROCEDURES FOR RECEIVING AND INSPECTION OF MATERIALS
(Receiving and Inspection Report Procedures (R.I.R))

PURPOSE
This procedure outlines the activities and responsibilities involved in the receipt and inspection of purchased product.

SCOPE
This procedure applies to the receipt and initial evaluation of incoming components, materials, and other product; preparation of the receiving and inspection report; quarantining of received items; and the inspection and accept/rejection of items.

CONTENTS
1. Procedure
2. Flow Chart
3. Sample Forms

REVISION RECORD

<table>
<thead>
<tr>
<th>REV.</th>
<th>DESCRIPTION</th>
<th>ORIGINATOR</th>
<th>Q.A</th>
<th>OPER. MANAGER</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ORIGINAL ISSUE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>REVISED</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1.0 PROCEDURES FOR RECEIVING AND INSPECTION

1.1 Responsibilities of Receiving Clerk.

1.1.1 Sign for items received.

1.1.2 Verify numbers of packages, check for obvious shipping damage and verify identification of packages to bill of lading.

1.1.3 Record information in receiving log and assign sequential receiving number.

1.1.4 Obtain packing slip from container of items.

   A. Attach to bill of lading, if available.

   B. Stamp receiving date on package slip.

   C. Obtain receiving copy of purchase order from file.

   D. Verify count, hidden damage and identification of items to packing slip.

      If there is a problem, refer information to supervisor for resolution.

   E. Circle quantity on packing slip.

   F. Record receiving number on packing slip.

1.1.5 Production items.

   A. Prepare part 1 of the receiving and inspection report (RIR). Use receiving number as RIR number.

   B. Record receiving number on yellow quarantined tag and attach to item.

   C. Move parts to quarantine area.

   D. Send RIR to inspection.

   E. Send packing slip to purchasing.
1.1.6 Non production items.
   A. Send packing slip to purchasing.
   B. Move material as per purchase order.

1.2 RESPONSIBILITIES OF RECEIVING INSPECTION

1.2.1 Receive RIR.

1.2.2 Obtain parts from quarantine area.

1.2.3 Obtain necessary instruction documents, such as specification sheets and purchase orders from Q.C. files and uncontrolled drawings from engineering files.

1.2.4 Perform inspection in accordance with instructions.

1.2.5 Record results of inspection on part II of RIR, sign, and date.

1.2.6 Fill out inspection log.

1.2.7 File original of RIR by receiving number.

1.2.8 If incoming materials are accepted:
   A. Prepare green approval tag and attach tag to container, or item as appropriate.
   B. Destroy yellow quarantine tag.
   C. Return parts to quarantine area.
   D. Discard pink copy of RIR.
   E. Send yellow copy of RIR to material handler.

1.2.9 If incoming materials are non-conforming:
   A. Prepare red rejection tag and attach to container, or item, as appropriate.
   B. Destroy yellow quarantine tag
   C. Return parts to quarantine area.
   D. Send pink and yellow copies of RIR to purchasing.
Shipment arrives

Receiving clerk:
1. Sign for items received
2. Verify no. of packages, check for damage, check identity against bill of lading
3. Record information in receiving log & assign sequential receiving number
4. Attach packing slip to bill of lading
5. Stamp receiving date on packing slip

OK?  

No  

Receive Dept. copy of P.O.  

Yes

Receiving clerk:
1. Open pkg., verify count, identity to packing slip and P.O. and check for hidden damage
2. Circle quantity on packing slip
3. Record receiving no. on packing slip

OK?  

No  

Contact supervisor to resolve

Yes

Production item?  

No  

Dispose of material as per P.O.

Yes

Receiving clerk:
1. Prepare part 1 of RIR
2. Record receiving no. on yellow quarantine tag and attach to item

RIR  

Goods  

Packing Slip  

A  

B  

C
Receiving inspector:
1. Perform inspection in accordance with instructions
2. Record results on part 2 of RIR; sign & date RIR
3. Fill out inspection log

OK?  Yes  No

Receiving inspector:
1. Prepare green approved tag & attach to container, item, etc.
2. Remove & destroy yellow tag

Pink & Yellow RIR

Yellow & RIR

Goods

Pink tag

Yellow tag

Trash

Material handler

Quarantine

Purchasing
Receiving Clerk ______________________________________ Date ____________ Sheet No. 6 of 9

<table>
<thead>
<tr>
<th>Received From</th>
<th>Via</th>
<th>No. Pkgs.</th>
<th>Weight</th>
<th>Quantity</th>
<th>Description of Goods</th>
<th>P.O. OR Req. No.</th>
<th>Charge Paid</th>
<th>Delivered to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remarks:

__________________________________________________________________________
<table>
<thead>
<tr>
<th>Received From</th>
<th>Via</th>
<th>No. Pkgs.</th>
<th>Weight</th>
<th>Quantity</th>
<th>Description of Goods</th>
<th>P.O. OR Req. No.</th>
<th>Charge Paid</th>
<th>Delivered to</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Remarks: ________________________________
# RECEIVING & INSPECTION REPORT

No. A

## PART I - RECEIVING

<table>
<thead>
<tr>
<th>SUPPLIER:</th>
<th>P.O. NO:</th>
<th>Date:</th>
</tr>
</thead>
</table>

Description

Remarks

## PART II - INSPECTION

Inspected by ____________________________

Conformance to Specifications

<table>
<thead>
<tr>
<th>Lot Size</th>
<th>Physical Damage</th>
<th>YES</th>
<th>NO</th>
<th>Electrical</th>
<th>YES</th>
<th>NO</th>
<th>Markings</th>
<th>Dimensions</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Qty.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Accepted ______ Date ____________ Rejected ______ Date ____________

____ Place in Stock

Cause for Rejection ____________________________

____ Forward to Next Operation


## PART III PURCHASING

Rejected Parts Disposition  Conditional Acceptance Approvals

Return to Supplier __________________ Remarks: Mfg. _____ Eng. _____ Q.C. ________

Comments: ____________________________________________
# Daily Inspection Log

<table>
<thead>
<tr>
<th>DATE</th>
<th>RIR NUMBER</th>
<th>ACC-REJ</th>
<th>REJ/ACC S/D</th>
<th>DATE</th>
<th>RIR NUMBER</th>
<th>ACC-REJ</th>
<th>REG/ACC S/D</th>
<th>COMMENTS</th>
<th>SPECIAL DISPOSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUARANTINED</td>
<td>RIR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>APPROVED</th>
<th>RIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product or Material</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part or Spec #</th>
<th>Quantity</th>
<th>Author</th>
<th>Date</th>
</tr>
</thead>
</table>

Remarks

<table>
<thead>
<tr>
<th>REJECTED</th>
<th>By Quality Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product or Material</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Part or Spec #</th>
<th>Quantity</th>
<th>Author</th>
<th>Date</th>
</tr>
</thead>
</table>

Remarks
MATERIAL LOT IDENTIFICATION

PART NO. __________________________ REV. __

DESC. ___________________________

LOT CONTROL NO. ___________________________

EXPIRATION DATE ___________________________

QTY. THIS CONTAINER ___________________________

DATE TO STOCK ___________________________ RECEIVED BY ___________________________

CAUTION

TRACEABLE COMPONENT

MUST BE ISSUED
BY LOT NUMBER!
RECORD LOT NUMBERS ON
ISSUING DOCUMENT!

CAUTION

TRACEABLE COMPONENT

Part No. ___________________________

Desc. ___________________________

Lot Control # ___________________________

Quantity ___________________________

STOCK REQUISITION

For Dept. __________

Date ___________________________

Is this material for: 
[ ] Replacement of Defective Mat'l
N.O.D. # ___________________________
[ ] Kit Error
[ ] Bulk Issue
[ ] Sales Order No. ___________________________
[ ] Test Inv.
[ ] ECN No. ___________________________
[ ] Other

<table>
<thead>
<tr>
<th>PART NUMBER</th>
<th>BIN CTRL</th>
<th>Posted</th>
<th>ORDER QTY.</th>
<th>ISSUED QTY.</th>
<th>BACK ORDER QTY.</th>
<th>LOT CONTROL NUMBER</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If stock-out items to be back ordered check box [ ]

FILLED BY ___________________________

PRODUCTION CONTROL APR'L ___________________________

DATE ___________________________

REQUISITIONER ___________________________
# RECEIVING REJECTION NOTICE

<table>
<thead>
<tr>
<th>VENDOR NAME</th>
<th>PART NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PART NAME</th>
<th>P.O. NUMBER</th>
<th>QUANTITY RECEIVED</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DATE RECEIVED</th>
<th>RECEIVING NUMBER</th>
<th>DATE INSPECTED</th>
<th>INSPECTOR</th>
<th>CROSS/REF.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## INSPECTOR’S REPORT

<table>
<thead>
<tr>
<th>ITEM</th>
<th>SPECIFICATION</th>
<th>SAMPLE PLAN</th>
<th>NUMBER OF DEFECTS FOUND</th>
<th>DESCRIPTION OF DEFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AQL</td>
<td>SAMPLE SIZE</td>
<td>ALLOW DEF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## PRELIMINARY REVIEW

<table>
<thead>
<tr>
<th>CHECK</th>
<th>DISPOSITION</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RETURN TO SUPPLIER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>USE AS IS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MATERIAL REVIEW BOARD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTHER</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QC. DATE</th>
<th>M.C. DATE</th>
<th>PURCHASING DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## MRB DISPOSITION

<table>
<thead>
<tr>
<th>CHECK</th>
<th>DISPOSITION OF LOT</th>
<th>ITEMS INVOLVED</th>
<th>AMOUNTS INVOLVED</th>
<th>MRB AUTHORIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EFFECTED RETURN TO SUPPLIER FOR REPAIR OR REPLACEMENT</td>
<td></td>
<td></td>
<td>MRB</td>
</tr>
<tr>
<td></td>
<td>USE AS RECEIVED WITH LIMITATIONS LISTED ON B.O.</td>
<td></td>
<td></td>
<td>Q.C.</td>
</tr>
<tr>
<td></td>
<td>USE AS RECEIVED. DEF LIMITATIONS LISTED UNDER COMMENTS</td>
<td></td>
<td></td>
<td>ENG.</td>
</tr>
<tr>
<td></td>
<td>ACCEPT PENDING SPECIFICATION CHANGE PER E.D.</td>
<td></td>
<td></td>
<td>OTHER.</td>
</tr>
<tr>
<td></td>
<td>SCREEN AND/OR REWORK BY PURCHASING NOTIFY SUPPLIER OF COST</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OTHER (SPECIFY BELOW UNDER COMMENTS)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

COMMENTS

Acceptance for future shipments will depend on proper completion and return of this report by supplier within 14 days.

<table>
<thead>
<tr>
<th>CAUSE OF DISCREPANCY</th>
<th>CORRECTIVE ACTION TAKEN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EFFECTIVE DATE</th>
<th>SIGNATURE &amp; TITLE</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. LABELING

LABELING REGULATIONS
- Misbranding
- False or Misleading Labeling
- Adequate Directions for Use
- Prescription Devices
- Sterile Devices

DESIGN OF LABELING
- Write to the Reader
- Refer to Actual Device
- Obvious Identification of Controls
- Don't Distract Reader
- Short and to the Point
- Gobbledygook
- Introduce Each Item
- Accentuate Key Terms
- Select Words Wisely
- Test Labeling
- Label Integrity
- Approval Policy and Procedure
- Design Transfer
- Production Controls
- Receipt and Inspection
- Area Separation and Inspection

STORAGE
- Label Check and Record
- Control Numbers
- Access Restriction

CHANGES

SHIPPING FOR PROCESSING

OVER-LABELING

exhibits
- Drafting and Approval of Labeling
- Approval Form for Labeling, Advertising, Literature, etc.
- Administration Set Label
- Labeling Control Record
- Device History Record: OB/GYN (Plate)
- User/Reader Comments

LABELING REGULATIONS
Medical devices in commercial distribution in the U.S. shall be properly labeled according to laws and regulations enforced by the Food and Drug Administration (FDA). Specific labeling requirements for medical devices are contained in:

- The Federal Food, Drug, and Cosmetic (FD&C) Act;
- The Fair Packaging and Labeling Act;
- The Radiation Control for Health and Safety Act;
- Title 21 of the U.S. Code of Federal Regulations, Part 801 for general devices, and Part 809 for in vitro diagnostic products;
- Title 21 of the U.S. Code of Federal Regulations, Part 812.5 for investigational devices;
- Title 21 of the U.S. Code of Federal Regulations, Part 820 for design and manufacturing controls for labeling; and
- Title 21 of the U.S. Code of Federal Regulations, Part 1010 - Performance standards for electronic products. Also see Parts 1020 and 1040.

Section 201(k) of the FD&C Act defines the term "label" as "a display of written, printed, or graphic matter upon the immediate container of any article . . . ." Under Section 201(l) of the FD and C Act, the term "immediate container" does not include a package liner. Any word, statement, or other information appearing on the immediate container should also appear on the outside container or wrapper, if any, of the retail package or be easily legible through the outside container or wrapper. The label is not required to appear on the shipping carton.

Section 201(m) of the FD&C Act defines the term "labeling" as all labels and other written, printed, or graphic matter: (1) on the device or any of its containers or wrappers, or (2) accompanying the device. The term applies any time while the article is in interstate commerce, or being held for sale after shipment or delivery in interstate commerce. The term "accompanied" is interpreted liberally. It extends to posters, tags, pamphlets, circulars, booklets, direction sheets, fillers, etc., that may be displayed in proximity to the article or shipped to the user before or after shipment of the device.

The distinction between labeling and advertising, while both draw attention to the article to be sold, is often nebulous or superficial. Both are forms of publicity and are used for an identical purpose. An appellate court described the relationship between the two as follows: "Most, if not all, labeling is advertising. The term 'labeling' is defined in the Act [section 201(m)] as including all printed matter accompanying any article. Congress did not, and we cannot, exclude from this definition printed matter which constitutes advertising."

Section 502(f)(1) and (2) of the FD&C Act requires that device labeling bear adequate directions for use, operating and servicing instructions, and either adequate warnings against uses dangerous to health, or information necessary for the protection of users. All devices require directions for use unless specifically exempted by regulation. Conditions for exemption from this requirement are in 21 CFR 801, Subpart D.

**Misbranding**

Section 502 of the FD&C Act contains the misbranding provisions for drugs and devices. It states a device is misbranded under a number of different circumstances, including:

- Its labeling is false or misleading.
- Its packaging does not bear a label containing the name and place of business of the manufacturer, packer, or distributor,
and an accurate statement of the quantity of contents.

- Words, statements, or other required information are not prominent on the labeling or are not stated clearly.

- It is intended for human use, and the label fails to bear the name and quantity or proportion of any narcotic or habit-forming substance contained in the product, and fails to display the statement, "Warning: may be habit forming."

- Its label does not contain adequate directions for use. These include warnings against use in certain pathological conditions; against use by children where its use may be dangerous to health; and against unsafe dosage, methods, duration of administration or application unless exempt as unnecessary to protect the public health.

- It is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling.

- It does not comply with the color additive provisions listed under Section 706 of the FD&C Act.

The Medical Device Amendments expanded the authority of the FD&C Act over misbranded medical devices. These amendments contain further circumstances under which a device is misbranded:

- The device's established name (if it has one), name in an official compendium, or including common or usual name, is not printed prominently in type at least half as large as used for any proprietary name.

- The device is subject to a performance standard and it does not bear the labeling requirements prescribed in that standard.

- There is a failure or refusal to comply with any requirement prescribed under Section 518 on notification and other remedies; failure to furnish material or information requested by or under Section 518; or failure to furnish any materials or information requested by or under Section 519 on records and reports.

- The device is commercially distributed without FDA concurrence on a 510(k) premarket notification submission.

**False or Misleading Labeling**

Section 502(a) states that a drug or device is misbranded if its labeling proves false or misleading in any particular. It is not a necessary condition that the labeling should be flatly and blatantly false for the FDA to take action. The word "misleading" in the FD&C Act means that labeling is deceptive if it creates or leads to a false impression in the mind of a reader. A "false impression" may result not only from a false or deceptive statement, but may be instilled in the mind of the purchaser by ambiguity and indirection. It might be caused by failure to inform the consumer of facts that are relevant to those statements actually made. In other words, the label that remains silent as to certain consequences may be as deceptive as the label that contains extravagant claims. Examples of misleading labeling include: ambiguity; half truths; trade puffery; expressions of opinion or subjective statements; and failure to reveal material facts, consequences that may result from use, or the existence of difference of opinion.

In the past, labeling found by the agency to be objectionable has featured such practices as: deceptive pictorial matter; misleading testimonials; misleading lists of parts or components; and brand or trade names instead of "established names" (see Sections 201(h), 502(e)(2), and 508 of the FD&C Act). Examples of false representations are:

- incorrect, inadequate or incomplete identification;

- unsubstantiated claims of therapeutic value;

- inaccuracies concerning condition, state, treatment, size, shape, or style;
● substitution of parts or material;

● subjective or unsubstantiated quality or performance claims; and,

● use of the prefix U.S. or other similar indication suggesting government or agency approval or endorsement of the product.

Adequate Directions for Use

Title 21, CFR Part 801.5, defines "adequate directions for use" as "directions under which the layman can use a device safely and for the purpose for which it is intended." See Part 801.4 for a definition of "intended use."

Among other reasons, directions for use may be inadequate because there is partial or total omission or incorrect specification of one or more of the following items:

● Statement of all conditions, purposes, or uses for which the device is intended. This includes conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising. This statement also includes conditions, purposes, or uses for which the drug or device is commonly used. These statements should not refer to conditions, uses, or purposes for which the drug or device can be used safely only under the supervision of a practitioner licensed by law; those conditions, uses, and purposes may only be referred to in advertisements directed to a licensed practitioner.

● Quantity of dose including usual quantities for each intended use and usual quantities for persons of different ages and physical conditions.

● Frequency of administration or application.

● Duration of administration or application.

● Time of administration or application in relation to meals, onset of symptoms, or other time factors.

● Preparation for use, adjustment of temperature, or other manipulation or process.

Prescription Devices

Labeling exemptions for prescription devices are in 21 CFR Part 801.109. These are devices which because of a potential for harmful effect, potential for misuse, or the collateral measures necessary to use, are not safe except under the supervision of a practitioner licensed by law. Hence "adequate directions for use" cannot be prepared for these devices. They are exempt from Section 502(f)(1) of the FD&C Act provided that all conditions specified in the labeling regulation are met.

These conditions state that the device shall be in the possession of a person, or his or her agents, or employees regularly and lawfully engaged in the manufacture, transportation, storage, or wholesale distribution of prescription devices; or in the possession of a practitioner such as a physician, dentist, or veterinarian licensed by law to use or order the use of these devices. These devices can be sold only to, on the prescription of, or by order of such practitioner for use in the course of their professional practice.

The label of the prescription device, other than surgical instruments, is required to bear:

● the statement "Caution: Federal law restricts this device to sale by or on the order of a _____", the blank to be filled with the word "physician", "dentist", "veterinarian", or with the descriptive designation of any other practitioner licensed by
the law of the State in which he or she practices to use or order the use of the device; and

- the method for its application or use.

Labeling on or within the package from which the device is to be dispensed shall also bear information for use under which practitioners licensed by law to administer the device can use the device safely and for the purposes for which it is advertised or represented. This labeling information includes indications, effects, dosages, routes, methods, frequency, and duration. Safety labeling includes relevant information on hazards, contraindications, side effects, and precautions.

When a device is capable of producing serious injury, even when used by a person thoroughly familiar with its operation, the directions for use shall provide detailed information. FDA has specific regulations on the labeling of intrauterine contraceptive devices, 21 CFR 801.427, and for diagnostic x-ray devices, 21 CFR 1020.30(h). In addition, FDA has issued general guidances for labeling certain devices, i.e., transcutaneous electrical nerve stimulators and electronic muscle simulators.

Where appropriate, directions for use should be supplemented with adequate warnings against the use of the drug or device under certain conditions. Any caution statement, similar to the directions statement, may appear in the labeling of the product; it is not necessary that it be printed on the label. In each instance, the responsibility for the adequacy of the warning statement appearing on the labeling rests with the manufacturer or distributor. For some devices, there are national consensus standards that specify that certain caution statements be on the device. There is no list of prescription devices in the CFR.

Sterile Devices

Special attention should be given to the labeling of sterile devices. For example, sterility may be needed only for a portion of certain devices and this condition should clearly be identified in the labeling. Devices that are not sterile in their entirety should be labeled to properly inform users what is actually intended to be "sterile" in the package. For example, a possible limiting statement might be:

"Caution: Only the fluid path of this set is sterile and nonpyrogenic. Do not use in a sterile or aseptic area without proper precautions."

The label of multi-device kits or packages containing a combination of sterile and nonsterile products will be considered to be false or misleading if it implies that all contents are sterile.

Some devices are intended to be sterilized by the user before use. In this situation, the labeling should provide adequate information about a suitable method of sterilization and any precautions or safeguards to be followed. For example, the labeling should describe any:

- special cleaning methods required;

- changes in the physical characteristics of the device that may result from reprocessing which affect its safety, effectiveness, or performance; and

- limit on the number of times resterilization and reuse can be done without affecting the safety or effectiveness of the device.

In the case of single-use sterile devices, many manufacturers include labeling to advise against resterilization and reuse. Some devices are not designed or constructed to be recleaned, and may not be capable of withstanding the necessary recleaning and resterilization procedures. Where reuse is common practice, manufacturers are encouraged to provide the information described in the above list.

The need for users to have instructions on how to open a sterile device package to avoid contamination of the device also needs
to be evaluated. When necessary, such instructions should be included in the labeling.

If a manufacturer modifies a device, the manufacturer should also review the labeling to ensure that it reflects current revisions and specifications. Thus, change control forms should contain a check off box for labeling and packaging. Some manufacturers identify labeling with a drawing number plus a revision code or date as an aid in identifying current labeling. The package insert or other labeling for in vitro diagnostic products is required to contain the revision date [21 CFR 809.10(b)(15)].

Shelf-life dating solely for package integrity and sterility is not usually required for general medical devices. There may be a need for expiration dating when a particular component of a device, such as a battery or diagnostic reagent, has a finite useful life. Labeling for in vitro diagnostic devices [809.10 (a) and (b)] requires an expiration date or some other means by which users may be assured of quality at the time of use. This requirement applies to both sterile and nonsterile in vitro diagnostic devices.

Although not required by regulation, most manufacturers of complex devices and sterile devices voluntarily use lot or serial numbers for production control and, if the need arises, to expedite failure investigations, repairs, modifications, or recalls. Lot, batch, or other control numbers are required for:

- implantable and life sustaining devices [820.65, Traceability];
- some products subject to radiological health standards [1002.30(b)(1), Records to be maintained by manufacturers]; and
- in vitro diagnostic devices [809.10(a)(9), Labeling for in vitro diagnostic products].

DESIGN OF LABELING

Various sections of the Quality System (QS) regulation have an impact on labeling including: section 820.30, Design controls; section 820.80, Receiving, in-process, and finished device acceptance; and section 820.70(f), Production and Process controls, which requires buildings to be of suitable design and have sufficient space for packaging and labeling operations. Section 820.120 deals with specific requirements for device labeling. These sections apply controls to the labeling content to meet the needs of the user and patient, as well as to meet the labeling specifications contained in the device master record. Applying the regulations to the physical design applications of labeling assures legibility under normal conditions of use over the expected life of the device. It also helps assure the proper inspection, handling, storage, and distribution of labeling. The requirements in 820.30(c), Design input, address the intended use of the device, and the needs of the user and patient.

Labeling includes equipment labels, control labels, package labels, directions for use, maintenance manuals, etc. The displays on CRTs and other electronic message panels are considered labeling if instructions, prompts, cautions, or parameter identification information are given.

Adequate labeling for a medical device requires proper design and procurement of the labels and labeling. Design includes generating the content of labels and labeling and making sure the content meets FDA requirements as well as the needs of the customer. To achieve these goals a number of concepts must be kept in mind such as: writing to the reader, referring to the actual device in labeling, obvious identification of the controls used, etc. Design controls for label integrity are discussed later.

There are some basic guidances, rules, and practices that can be used to immediately improve writing. The following paragraphs will discuss them, with emphasis on how they can be used to make labeling clear and comprehensible.

As an essential aid, writers are encouraged to obtain a copy of 40,000 Words published by Webster's New World Dictionary or a similarly titled book by any of the reference-book publishing companies. Most of these reference books have about four pages of punctuation rules. Using these pages of rules can immediately improve not only the style and clarity but also the accuracy of your writing. Writers are also encouraged to obtain and use a standard college-level text on technical writing.

Write to the Reader
The most serious problem is that writers tend to write to themselves. Their material is clear to them so they mistakenly think it is as clear to others. For example, the sensitivity control on an instrument is called "gain" control on page one of the instruction manual, "amplitude" control on page two, and "level" control in the next section. Further, the photograph in the introduction shows the same control with a call-out identification note labeled "Signal Adjust." No wonder readers get confused! Yet the author of the example knew what he was trying to write about and, most certainly, he was writing to himself.

When writing labeling, especially for an over-the-counter (OTC) device, the author must know the reading level of the target audience. If data on reading levels is not available, this may necessitate reader interviews to establish a reading level for the target audience. If the device is designed for home use, a useful guide is Write It Right available through DSMA.

Refer to Actual Device

One simple way to reduce control identity confusion as described above, reduce other types of labeling errors, and increase clarity is for authors to keep a labeled instrument, kit, or photograph(s) nearby and refer to it as they write. It is easier to write the truth when you know the truth. Make sure the terminology and descriptions in the labeling match that on the actual device. It is best to always use the same title for each given item or control throughout the manual, insert, label, and advertisement. Likewise, the same title should be used in charts, figures, or screen displays such as cathode-ray tubes, LCD panels, etc.

Obvious Identification of Controls

Because the title of controls or other items in screen displays and other labeling should be exactly the same as in the labels on equipment, reagents, accessories, etc., authors may need to develop and use an appropriate correlation technique for corresponding titles in instruction manuals, package inserts, etc. One common and simple technique is to use all capitals for the titles of controls in labeling. For example:

```
OFF ← ON
POWER SWITCH
PRESS FOR HEAT
READY LAMP
```

The associated text, for example, might state:

Flip the POWER SWITCH to ON.

In about three seconds, the READY LAMP will illuminate.

Now press the HEAT button to switch the heater on.

With this correlation technique, the words "on" and "off" are capitalized in the labeling only when they actually appear on the instrument control panel. Note that "ON" is capitalized in "POWER switch to ON" as the actual switch has "POWER," "ON," and "OFF" printed by it. In contrast, note that "on" is not capitalized in the statement "to switch the heater on" as it is not a label of a control on the device. Also, be careful to use a simple correlation system that is readily apparent to the intended audience.

Don't Distract Reader

Readers are very busy trying to learn how to use a new device. They should not be annoyed by any unnecessary distractions such as:
changes in format,
unusual typeface,
incorrect page numbers, and
incorrect figure numbers.

For a person trying to read in a hurry, a font such as script can be a major distraction; therefore, it is best not to use script, italics,
or any other unusual or hard-to-read type-faces. Remember, you have decided to write for the benefit of the intended audience. Forget about your personal preferences and use only the most common fonts. Also, select a type size that is readable at the intended distance. For example, labeling displayed on the screen of a wall-mounted heart monitor should be readable from several feet away. Also, use a consistent format throughout the document. Check the format and section titles against information on the contents page. In some cases, such as for in vitro diagnostic products, the arrangement of information in the labeling may be dictated by a regulation. Page numbers should not be referenced in instruction or service manuals. It is too easy for the actual page numbers to be changed during the original writing or when the manual is updated. It is much better to refer to paragraph titles or numbers as these are less likely to change; and, if changed, titles are more noticeable by writers and typists than are page numbers. The use of correct figure numbers is easy -- just check them.

**Short and to the Point**

It is important to use sentence structure that will convey the intended message with a minimum of misinterpretation or need to reread. Tests have been conducted to determine the ability of readers to follow instructions in a sentence based on the number of activities to be performed. The average person's ability to follow instructions decreases rapidly when a sentence contains more than two facts. (Keep in mind your own experiences in reading instructions.) Therefore, sentences in labeling need to be short and to the point. Avoid long strings of adjectives and be specific. Try to be as specific as possible with your instructions. For example, "ambient" or "room temperature" generally should not be used. Instead specify the desired or necessary range of operating conditions. In many cases a list of activities to be performed is better than burying the facts in long sentences. A numbered list is better if the user may have to repeat any part of the procedure. If it takes lots of words to get to the point, the reader will probably miss the point! Short, choppy sentences are acceptable in instruction manuals and other labeling. You are not trying to entertain readers with beautiful, flowing prose -- rather, you want to catch their attention with key facts so they correctly perform the specified instructions. Thus, use short sentences, get to the point, be specific, and keep graphics and pictures near the corresponding text.

**Gobbledygook**

Another way to be more specific and shorten sentences is to avoid "gobbledygook." The following terms were collected from actual instruction manuals:

<table>
<thead>
<tr>
<th>ORIGINAL</th>
<th>PREFERRED EQUIVALENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Makes provisions for</td>
<td>*</td>
</tr>
<tr>
<td>Serves to</td>
<td>*</td>
</tr>
<tr>
<td>At the time of</td>
<td>When</td>
</tr>
<tr>
<td>In conjunction with</td>
<td>And</td>
</tr>
<tr>
<td>Carried out in</td>
<td>Perform</td>
</tr>
<tr>
<td>Comes up to</td>
<td>Reaches</td>
</tr>
<tr>
<td>Will also serve as a chance to</td>
<td>May</td>
</tr>
<tr>
<td>Will be sure that will</td>
<td>Ensure</td>
</tr>
<tr>
<td>Available through the use of</td>
<td>*</td>
</tr>
<tr>
<td>Care should be used so as not to</td>
<td>Be careful</td>
</tr>
<tr>
<td>Be provided for positive determination</td>
<td>*</td>
</tr>
</tbody>
</table>
Causes power to be applied to
Switches power to
Due to the fact that
Because
Take the form of
Be

In most cases, the equivalent term in the list can replace the original term. For the asterisked items, the equivalent is simply a direct statement of what is intended. Of the terms listed, the combination most often used is "makes provision for." Simply eliminating "makes provision for" and "be provided for" from labeling will result in an immediate improvement for readers.

**Introduce Each Item**

Always introduce each control, indicator, device, or subject before it is discussed in the text. The introductions should be brief and may be very brief. Keep in mind the items will be described in more detail later. Abbreviations and new or uncommon terms should be defined. The introductions and definitions prevent readers from going into mental shock, breaking their train of thought, and asking: What is this? By then readers have probably forgotten the last two or three facts read. Also, readers may wonder about any "cliff-hanging" item when they resume reading. This disturbance may detract readers from fully assimilating the next instructions being read. To avoid distractions and confusion, a writer of labeling should always:

- introduce each item, and
- define new or uncommon terms.

With respect to definitions, a writer should never give a new meaning to an existing common term in the language. To avoid this disservice, coin a special term or code number such as Class Q, Code 1, or Level 2.

**Accentuate Key Terms**

Whenever it is stated in instructions that something shall be done, then "shall" should be set in bold type, or otherwise delineated. Likewise, caution and warning statements should be emphasized by boxing, bold type, etc. Underlining should not be used as it makes the descending part of a letter hard to read and appears to be top lining on some printers. Refer to any regulations or standards for a specific product and use the recommended or required caution statements. When standard terminology exists in a consensus standard, creating new caution statements is not advisable. Confusion is less likely to occur when one stays with the commonly understood terminology.

**Select Words Wisely**

When large print is needed for reading at a distance or to attract attention to signs, caution labels, and screen prompts, words generally should be short in order to fit the available space. This rule also applies to the wording on control labels. This situation places a burden on the writer to select terms that convey the desired message. Consider the following wording from two actual highway signs:

| PLANT TRAFFIC ENTERING HIGHWAY | NO FISHING OFF BRIDGE |

Have you ever been run over by a pachysandra? If you can't fish off the bridge, does that mean you are allowed to fish only on or from the bridge? Better choices for the intended messages are: "Traffic entering highway" and "No fishing from bridge".

**Test Labeling**

Finally, always have someone not familiar with the product operate it exactly according to the draft instructions, labels, screen displays, etc. You should not do any coaching because coaching destroys the validity of the trial. By coaching you transfer your
"memory" to the user. Therefore, no coaching -- this is the "acid" test -- good luck! During the trials, note any significant problems and make appropriate corrections to the instructions, prompts, or other labeling.

**Label Integrity**

All labels shall be designed and applied to devices and containers so that the labels will remain in place and legible during the customary conditions of distribution, storage, and use [820.120(a)]. Likewise, other labeling such as user instructions should remain legible during customary storage and use. For example, labeling printed by machines onto plastic in vitro diagnostic media plates is often smeared and thus is inadequate [FD&C 502(f)]. The manufacturers of such devices should assure that the print is legible and will remain legible until used.

Many magazines use "wet" ink which smears when touched by sweaty or oily fingers. Obviously, this type of ink will not meet the design requirements for package inserts, instruction manuals, and the like.

Labels may be mounted by adhesives, screws, rivets, drive screws, etc., or printed or etched onto panels and/or onto controls. The labels should be located so that they will be seen but not be abraded during use. (Many of us have seen the unbelievable cases where safety labels on ladders and riding lawnmowers were placed in the foot rest areas. Of course, they were worn off after a few uses!)

**Approval Policy and Procedure**

The review of labeling from the design stage through to the finished device should be documented like the review of other significant components. This includes the labeling development, any changes, and final approval. Documentation should be included in the design history file of the procedures used, signature of the responsible person, and date. Because several activities are performed and controlled during the development and use of labeling, Table 11.1, "Drafting and Approval of Labeling" and "Final Approval of Labeling, Advertising, Etc." are presented as guidances. This table contains a typical sequence of events required to develop and control labeling. Other controls are discussed below.

Before release for use, labeling should be reviewed and approved by product development, service, marketing, quality assurance, and other appropriate managers (820.30). Manufacturers need to have a policy/procedure which covers the drafting, review, and approval of labeling. Approval forms are generally used in conjunction with such a policy/procedure. A sample approval form and procedure are presented at the end of this chapter. Other procedures and forms such as "Change Control" are referenced in this procedure. Note that this procedure also covers other elements such as a correct device master record, correct transfer of labels into production, lot control, change control, etc. Samples of various procedures appear at the end of chapters throughout this manual.

**Design Transfer**

Specifications are required in the device master record for the content and physical design parameters of labels. (see Chapter 8). Labeling specifications include the engineering drawing and/or artwork for each label, appropriate inspection or control procedures, and appropriate procedures for attaching the labels. All procedures, drawings and artwork should have the name of the preparer, an approval signature, and a date. The approval signature, date, etc., may be on the back side of artwork or on a label approval form. Further, artwork may contain only an identification code or title if the "content" of the artwork is duplicated on approved engineering drawings, adequately identified, or cross-referenced with respect to the label approval form. That is, a manufacturer should be able to identify isolated artwork.

Hardcopy labels, package inserts, and similar labeling are also specified and purchased as components (see Chapter 8). For correct purchase and use of labeling, specifications are usually stated on engineering drawings and/or purchase specifications. Thus, artwork or "copy" alone will not fulfill the device master record and purchasing control requirements for labeling except for the most simplistic labeling such as brief errata sheets.
The engineering drawings or purchase specifications should specify, as appropriate, the label substrate, dimensions, ink, finish, mounting method, etc., so that the purchased label will remain attached and legible during the customary conditions of processing, storage, handling, distribution, and use.

<table>
<thead>
<tr>
<th>PHASE</th>
<th>SECTION</th>
<th>CONTROL ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Design</td>
<td>820.30, 820.120 &amp; 820.130</td>
<td>Meets needs of user and intended use. Text review. Quality of mounting such as rivets, adhesives, etc. Quality of ink, anodize, etc. Content per 21 CFR 801 and 809 company claims and standards.</td>
</tr>
<tr>
<td>2. Verification/Validation</td>
<td>820.120, 820.75 &amp; 820.30</td>
<td>Simulated or actual processing such as sterilization, shipping tests, label affixing, etc. Saline, alcohol, and coffee spill tests?</td>
</tr>
<tr>
<td>3. Changes</td>
<td>820.30 &amp; 820.75</td>
<td>Establish and maintain approval procedures.</td>
</tr>
<tr>
<td>4. Documentation</td>
<td>820.30, 820.181 &amp; 820.120(e)</td>
<td>Approve, date and change control label drawings. A key label shall contain the control number of the finished device either on or accompanying device.</td>
</tr>
<tr>
<td>5. Procurement</td>
<td>820.120(b) 820.180</td>
<td>Proofread before release to inventory stock. Record signature of proofreader and date.</td>
</tr>
<tr>
<td>6. Storage</td>
<td>820.120(c) &amp; (d)</td>
<td>Store labels to prevent mix-ups. Restrict access to authorized persons.</td>
</tr>
<tr>
<td>7. Separate operations</td>
<td>820.120(d)</td>
<td>Separate multiple operations to prevent mix-ups.</td>
</tr>
<tr>
<td>8. Area inspection</td>
<td>820.120(d)</td>
<td>Before beginning labeling operations, designee to inspect area and remove extraneous devices and labels.</td>
</tr>
<tr>
<td>9. Issuance</td>
<td>820.120(b), 820.120(e) &amp; 820.65</td>
<td>Examine for identity and, where appropriate, expiration date and control number. Record date and person examining labels.</td>
</tr>
<tr>
<td>10. File Sample</td>
<td>820.184(e)</td>
<td>Copy of primary identification label shall be in the device history record.</td>
</tr>
<tr>
<td>11. Inspection</td>
<td>820.80(d), 820.86 &amp; 820.80(e)</td>
<td>Inspect finished device per written procedure. Designee shall check all acceptance records and test results and see that requirements are met and records are present and complete.</td>
</tr>
</tbody>
</table>

Front panels, other instrument panels, meters, fuses, pushbuttons, and the like often are either labels or contain labels and thus should, as appropriate, meet device master record and control requirements. Component specifications, assembly drawings, and test/inspection procedures are appropriate controls to prevent mixup of meters, push buttons, and other labeled instrument controls.

Whether a manufacturer considers a software driven display to be labeling or data makes little difference under the QS regulation because, either way, the finished device labeling or data should meet the device master record specifications. When manufacturers develop and validate software, they should also review any electronic displays to see that the "labeling" meets all applicable requirements, such as adherence to specifications in the device master record, correct parameter identification, agreement with the instruction manual, and, of course, correct display of performance data.

**Production Controls**
When reviewing or auditing labeling operations, it is wise to keep in mind that the GMP requirements are flexible. The degree of labeling control needed to satisfy the QS regulation varies considerably for different devices and operations. In order to avoid wasting money and increasing the cost of health care, manufacturers need to give considerable and prudent thought to the appropriate level of control needed for their operations as allowed by 820.5. Information and guidances presented in this manual should aid manufacturers in making these decisions. The level of control needed should be reconsidered when products are changed. Likewise, the controls needed, and the success of the existing control program, should be reviewed during quality system audits (see Chapter 17).

Medical device manufacturers should incorporate in their quality system several elements that relate to labeling in order to meet the GMP requirements. The quality system should be adequate to assure that labeling reflects user needs, meets the device master record requirements with respect to legibility, adhesion, etc., and assure that labeling operations are controlled so that the correct labeling is always issued and used.

Receipt and Inspection

Upon receipt, all packaging and labeling materials, including preprinted containers, inserts, and preprinted packaging materials, should be examined and, if deemed necessary by the company, tested to assure conformance with specifications as discussed in Chapter 10, Purchasing and Acceptance Activities. Also, samples of labels, including labeled panels, meters, etc., shall be proofread by a designated individual(s). After being accepted by a responsible individual, these components may be placed into inventory or into production. These inspections shall be recorded in the device history record as required by 820.80(e) and 820.120(b) to show that inspection and proofreading were performed. The inspection record for device labeling should be kept simple.

Area Separation and Inspection

All labeling and packaging operations should be separated to the degree necessary [820.120(d)] to assure there are no mixups between similar products or labels. Separation may be either a physical or spatial separation or by performing the labeling and packaging at different times for different devices. Separation is not required when mixups are impossible, such as the case of labeled front panels that only fit the intended family of devices.

The likelihood of a labeling mixup determines how stringent production area controls should be. For example, label control need not be stringent if only one product or dissimilar products and labeling that are unlikely to create confusion are processed. Before beginning any packaging and labeling operation in which mixups could occur, the production area and equipment for the operation should be thoroughly examined to ensure that any devices and labeling materials remaining from previous operations have been removed. It is important to make certain that the surrounding area, tables, packaging lines, printing machines, and other equipment are cleared of labels and other materials used in the previous operation.

Unused labeling that contains pre-coded serial numbers, manufacturing dates, expiration dates, control numbers, etc., should be destroyed and not returned to the label storage area. The GMP requirements do not include reconciliation of the number of labels used with the number issued, although, this control is recommended for some devices, such as when different sizes of the same product are being packaged or otherwise labeled.

STORAGE

Where feasible, labels for similar devices should be designed with different shapes and colors to reduce the probability of mixups. Thereafter, all printed packaging and labeling materials, including preprinted containers, inserts, and preprinted packaging materials shall be stored in an area and manner suitable to prevent mixups [820.120(e)]. For example, if labels from one container are accidentally dropped, they should be stored so they will not fall into another container of similar labels. Labeling should be identified and segregated to the degree necessary to prevent mixing of similar labeling. Access to labeling should be limited to authorized personnel.
Storage control should be appropriate for the number and kind of devices. For example, a manufacturer that has only one product with one label does not need an elaborately controlled storage area. Similarly, a manufacturer with only a few types of devices having dissimilar labeling would not normally require stringent control.

One case that requires dedicated attention to storage and control is prelabeled "sterile" but not-yet-sterilized devices. Manufacturers should make absolutely certain that mixups cannot occur. Also, they should make certain that all samples used for market promotion are sterile or labeled with a manifest caution statement, because a packaged and labeled market-promotion sample might be used by the recipient. One approach is to sell sterile samples at zero cost so that such samples are subjected to all of the company product release and distribution controls. Quality awareness training is required by section 820.25. Marketing personnel should be informed of labeling control requirements and the consequences of a violation.

**Label Check and Record**

In summary, labeling should be carefully examined to assure that the contents of the labeling comply with the labeling specifications in the device master record. This examination should include any control numbers or expiration dates used on the labels. A record of this check, including the date and name of the person performing the examination, should be made in the device history record.

If expiration dates are used, they should reflect the time limitations within which the device is fit for its intended use when stored and used per its labeling. The manufacturer should have stability test data establishing how long the device will remain fit for use to support expiration dates.

If label mixups cannot occur -- for example, a manufacturer makes only one device or uses only one label -- and there are no control numbers or expiration dates, the original inspection when the labeling was placed into inventory is an adequate check for compliance with the device master record specifications. A second check need not be performed because it serves no purpose (820.5). If, however, there is any possibility that incorrect labeling can be used, a second check should be made when the labeling is issued for application, packaging, or shipping.

**Control Numbers**

Devices intended for surgical implant, and devices intended to support or sustain life and whose failure to perform properly can be expected to result in significant injury, shall contain a control number, serial number, letters, etc., for traceability (820.65). Procedures for establishing and maintaining control numbers shall be documented in the DHR. This means a control number for the finished device, and not the label itself. Although this control number may be on a label, most labeling also contains another number, such as a drawing number, for control of labeling configuration and procurement.

The control number for traceability need not be on every label on the device; however, the control number should appear on the primary label that goes to the ultimate user. The label on a shipping carton does not meet this requirement because bulk items may go to a central distribution point in the user-facility and the shipping carton will most likely be disregarded.

**Access Restriction**

Access to labeling should be restricted to authorized personnel. Labeling also should be stored in an adequately segregated area to minimize the chance of mixups. Segregation is recommended because it increases the control over the label storage area with no significant increase in cost.

**CHANGES**

Labeling is a component of the device and part of the device design output; therefore, all changes to labeling should be made under a formal change control system. Design changes shall meet 820.30(i); and other changes are made according to 820.40. Any changes to labeling should be formally reviewed and authorized before implementation. That is, follow the guidance in this
chapter as if new labeling is under development.

When making changes to primary aspects of a device and to primary documentation, the review group should determine if any secondary items such as labels or instructions are affected and also need changing. There should be a check-off block on change-order forms, or any other change control mechanism, for recording that the effect of the primary change on labeling was considered and appropriate action was taken. The failure of a change control system to alert employees of basic requirements is considered to be a serious deficiency in a quality system.

**SHIPPING FOR PROCESSING**

Devices that are prelabeled "sterile," but are not yet sterilized, require be controlled at the manufacturer and during shipment for further processing. Likewise, devices that have been sterilized and shipped to the manufacturer's warehouse or other controlled distribution point before final release should be properly labeled. The pallets, or designated unit, should be marked to indicate the status of the device, such as "non-sterile," "sterilized: awaiting test results," or an equivalent statement (820.86). The company should be able to show that it has control of the devices until final release and, could have them destroyed or returned for reprocessing if necessary. Unless so qualified, a distributor's warehouse or facility is not considered a controlled distribution point.

The QS regulation states that each manufacturer shall establish and maintain procedures to ensure that mixups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling (820.140).

The storage regulation at 820.150 states, "(a) Each manufacturer shall establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed as appropriate. (b) Each manufacturer shall establish and maintain procedures that describe the methods for authorizing receipt from and dispatch to storage areas and stock rooms."

Manufacturers of sterile devices commonly label devices as sterile at one establishment and ship them to another facility or a contract sterilizer for sterilization. Shipments of nonsterile devices labeled as sterile are clearly misbranded and adulterated, and if diverted into consumer channels, could create a potential health hazard. FDA recognizes that this longstanding practice is an economic necessity for many manufacturers. Therefore, to meet the needs of these manufacturers in a way that will also assure the protection of the public health, FDA added Part 801.150(e) to the Code of Federal Regulations (CFR). It is reprinted below.

(e) As it is a common industry practice to manufacture and/or assemble, package, and fully label a device as sterile at one establishment and then ship such device in interstate commerce to another establishment or to a contract sterilizer for sterilization, the Food and Drug Administration will initiate no regulatory action against the device as misbranded or adulterated when the nonsterile device is labeled sterile, provided all the following conditions are met:

1. There is in effect a written agreement which:

   (i) Contains the names and post office addresses of the firms involved and is signed by the person authorizing such shipment and the operator or person in charge of the establishment receiving the devices for sterilization,

   (ii) Provides instructions for maintaining proper records or otherwise accounting for the number of units in each shipment to insure that the number of units shipped is the same as the number received and sterilized,

   (iii) Acknowledges that the device is nonsterile and is being shipped for further processing, and

   (iv) States in detail the sterilization process, the gaseous mixture or other media, the equipment, and the testing method or quality controls to be used by the contract sterilizer to assure that the device will be brought into full compliance with the

(2) Each pallet, carton, or other designated unit is conspicuously marked to show its nonsterile nature when it is introduced into and is moving in interstate commerce, and while it is being held prior to sterilization. Following sterilization, and until such time as it is established that the device is sterile and can be released from quarantine, each pallet, carton, or other designated unit is conspicuously marked to show that it has not been released from quarantine, e.g., "sterilized -- awaiting test results" or an equivalent designation.

OVER-LABELING

Over-labeling by placing a new label over an old label is discouraged by FDA but is acceptable as long as the new label and its use meet GMP requirements [(820.30, 820.120, 820.90(b)(2)] for user needs, attachment, legibility, reprocessing, and change control. Over-labeling is also discouraged in some foreign countries.

EXHIBITS

Exhibits that cover labeling design and labeling control are presented on the following pages. These exhibits show how some GMP requirements for label control may be met. These procedures and forms may need to be modified to meet the needs of a specific operation.

Drafting and Approval of Labeling

This drafting and approval procedure is used to establish a uniform system for controlling the content of labeling and for approving labeling. This procedure is adaptable for use by any size manufacturer. The approval form which follows may be used with this procedure.

Approval Form for Labeling, Advertising, Literature, etc.

This form is intended for use by a medium to large manufacturer, however, the checklist style can be adapted even to a small manufacturer. The areas of concern are listed under the group that is responsible for that concern. Thus, every department has input into the acceptability of the labeling.

Administration Set Label

This example of a label for an administration set begins with a complete description of the device inside the package. The directions for use section is arranged so that each point in the directions for use is numbered and only one point is made for each step. The various points in the directions are short and to the point. Where emphasis is needed, as in the case of air bubbles, the information is bolded for further emphasis.

Labeling Control Record

This blank copy of a labeling control record shows what a sample form looks like. At the bottom of the form, there is space to attach the actual labeling used so that a comparison of the actual labeling used versus that required can be made during product release review.

Device History Record: OB/GYN (Plate)

The history record exhibited here is limited to the filling operation for a media product. The form has space to print the same label as printed on the plates during the filling operation for label control and release review. This technique eliminates human copying errors.
Feedback is an important element in any QA system. Whenever manuals or instructions form part of the labeling for a product, it is wise to solicit review from persons not familiar with the use of the product. These people can be employees of the manufacturer or, as in this exhibit, actual users of the product. The information received will reflect the problems encountered by persons trying to follow the instructions without any preconceived knowledge of the actual operation of the product.

1.0 PURPOSE

To establish a uniform procedure for controlling the content of labels and labeling and obtaining approval within our company.

To assure compliance with GMP requirements and with company policy directives.

2.0 SCOPE

Applies to all devices including those used for market research or clinical investigations.

Advertising material is excluded from this SOP. It is covered by our SOP #____, "Advertising Material Control and Approval."

3.0 REFERENCE DOCUMENTS

3.1 Food and Drug Administration LABELING, GMP, etc. requirements in 21 CFR Parts 800-1299.

3.2 SOP #____, Advertising Material Control and Approval

3.3 SOP #____, Change Control System

4.0 FORMS

4.1 Form SOP #____, Labeling Development and Verification Checklist

4.2 Form SOP #____, Labeling Approval Form

4.3 Form SOP #____, Engineering Change Order Form
6.0 PROCEDURE

6.1 Preparation and Approval

The Labeling Development and Verification Checklist should be used as a guidance for all activities because the finished labeling must be evaluated versus this checklist.

6.1.1 The need for a label or labeling is determined by an operating department such as Engineering, Marketing, Manufacturing, or Quality Assurance. Marketing, as appropriate, will conduct and document literature searches and perform design input market research to determine any special needs of the users. Design input, regulatory, safety, and other appropriate information shall be used to create a labeling specification.

6.1.2 The Engineering Department prepares a manuscript complete with illustrations or prepares a drawing(s) of the label showing the wording, label use, and/or location. The label may be on a front panel drawing or other engineering drawing.

6.1.3 When final prototypes and/or pilot production models are available, the labeling shall be verified and the results recorded on the Labeling Development and Verification checklist. If needed, appropriate corrective action shall be taken by the appropriate department. The completed checklist shall be filed with the device design verification records.

6.1.4 Before final approval, labeling will be discussed at appropriate design review meetings. The minimum attendees are the originator, Engineering, and QA.

6.1.5 The Engineering Services Department then prepares form SOP #______, Labeling Approval Form, and circulates it to the originating department, Training and Education, Marketing, and Quality Assurance for approval. (See the following sample approval form.)

6.1.6 Engineering Services will coordinate and file all labeling verification checklists, notes, approvals and approval forms in the design history file.

6.1.7 When approval is received from all parties, the label or manuscript is assigned a drawing number and is released and added to the product structure (DMR Index) following the Change Control System (SOP #______) procedure.

6.2 Implementation and Control

6.2.1 When labels or labeling are produced, Quality Control must proofread the material and verify that it is correct by first article inspection and so indicate by signing an appropriate document.

6.2.2 All labels and labeling will be reviewed by QA for lot control requirements. Each original document will be marked by Engineering Services to indicate the level of control required. At least one label on each device intended for surgical implant into the body or to support or sustain life must have a lot, serial, or other control number. See 820.65, Traceability.
7.0 EXPERIMENTAL DEVICES

7.1 Labels and labeling for experimental or investigational devices are required.

7.2 The documentation need not be as complete as for production labels and labeling; but, it **must** be adequate to allow procurement of the labels or labeling and adequate for the intended use. If appropriate, such labeling **must** meet 21 CFR 812.5.

8.0 CHANGES

8.1 Any changes to released labels or labeling are accomplished according to SOP #______, "Change Control System".

9.0 SCHEDULES

(Design QA requirements are presented below. There are also related production requirements.)

9.1 Drafts **must** be generated according to a schedule that allows a normal approval procedure. While urgent copy approval is occasionally necessary, it should not become standard operating procedure.

9.2 All labels **must** be approved according to the routine engineering schedule for components.

9.3 Labeling **must** be approved before or when the device is released for full-scale production. HOWEVER, any pilot units placed in commercial distribution must be labeled with approved pilot or final labeling.

9.4 The design review for any pilot lots and the design review of initial full-scale production lots **shall** include a design review of labeling.

   1. The design review records for labeling shall be identified for easy recall. These records shall be a part of the design history file.
# QSR MANUAL

## FINAL APPROVAL OF LABELING, ADVERTISING, Etc.

<table>
<thead>
<tr>
<th>Intended use/distribution</th>
<th>Doc. No.</th>
<th>Dwg. No.</th>
<th>Project Leader</th>
<th>Approval Coordinator</th>
</tr>
</thead>
</table>

| Yes No N/Applicable | | | | |
|---------------------| | | | |

### ENGINEERING
- Tech. specs., installation data, & part numbers correct.
- Procedural information is accurate and complete.
- Standards imposed by CSA, UL, IEC, etc. are met.
- Illustrations are technically accurate.
- Equipment protection cautions included where necessary.
- Procedures verified on final prototype or prod. model.
- Changes requested in draft have been made or negotiated.
- Procedures are safe and effective.
- Final draft has been proofread.

<table>
<thead>
<tr>
<th>Project Engineer:</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
<tr>
<td>Engineering Services Mgr.:</td>
<td>Date: / /</td>
</tr>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
</tbody>
</table>

### SERVICE
- Maintenance information is written for intended user.
- Lists part numbers needed for maintenance and repairs.

<table>
<thead>
<tr>
<th>Service Manager:</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
</tbody>
</table>

### TRAINING AND EDUCATION
- Document is adequate for training purposes.
- Document agrees with experience of training specialists, if experienced with this or similar products.

<table>
<thead>
<tr>
<th>Training Manager:</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
</tbody>
</table>

### MARKETING
- Material is effective and complete for intended use.
- Material meets the needs of the international market.
- Material is professional and projects the company image.
- All claims supported by verification data.

<table>
<thead>
<tr>
<th>Project Manager:</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
<tr>
<td>Director Marketing:</td>
<td>Date: / /</td>
</tr>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
</tbody>
</table>

### QUALITY ASSURANCE
- Hazards situations are highlighted with adequate warnings.
- All FDA labeling and GMP requirements, are met.

<table>
<thead>
<tr>
<th>Quality Engineer:</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Approval Coordinator</th>
<th>signature</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Form # Approved</th>
<th>Date: / /</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Approved</td>
<td>[ ] Not approved</td>
</tr>
</tbody>
</table>
MAJOR MEDICAL, INC.

ADMINISTRATION SET

Catalog Number 1403

With macro non-vented drip chamber, 80 inch length and "Y" site.

INSTRUCTIONS FOR USE

1. Prepare solution container.
2. Close side clamp and open ____ device.
3. Remove protector cap from drip chamber piercing spike.
4. Aseptically insert spike through set port of solution containers.
5. Squeeze and release drip chamber until solution half fills the drip chamber.
6. Open slide clamp and allow the tubing to fill with solution, thus eliminating all air bubbles. **DO NOT ALLOW AIR TO BE TRAPPED IN SET.**
7. Close slide clamp.
8. Make venipuncture with I.V. device of choice.
9. Open slide clamp.
10. Regulate rate of infusion with ____ device.
    Micro Set: 60 drops delivers about 1 ml; Macro Set: 15 drops delivers about 1 ml.
11. To stop flow without disturbing valve adjustment, use slide clamp.

PRECAUTIONS:

- Supplementary medication may be injected with 20 or 22 gauge needle into injection site.
- If fluid path is interrupted, take special care to ensure fluid path has not been contaminated.
- Do not use to administer blood, blood products, suspensions, emulsions or any medication not totally soluble in the solution being administered. These medications may be administered through the distal Y-injection site with slide clamp closed.
- Puncturing drip chamber or tubing can cause air contamination and leaking.

FOR SINGLE USE ONLY

CAUTION: Puncturing tubing can cause air embolism.

NONPYROGENIC

STERILE: Unless Package has been opened or damaged.

CAUTION: U.S.A. Federal law restricts this device to sale by or on the order of a physician.

STORE AT ROOM TEMPERATURE

Manufactured for:

Sterilized by E.T.O. Major Medical, Inc.
Date of Sterilization: Debbville, Maryland 20906
Lot No. ________ Printed in U.S.A.
LABEL CONTROL RECORD

1. Labeling area was inspected and no labels from previous operations were present.
   Initials: ______________________

2. Just before starting the labeling operation, labels were examined for correct:
   [ ] Identity   [ ] Expiration date on label   [ ] Control number
   Name: ______________________  Date: ______________________

3. REAGENT INFORMATION

   3.1. CONTAINER INFORMATION

   Description ______________________  Size ______________________
   Catalog Number ______________________  Type ______________________
   Stability ______________________  Quantity ______________________
   Lot Number ______________________  Other ______________________
   Reagent Expiration Date ______________________
   Initials ______________________  Date Recorded ______________________

4. [ ] Labels were correctly applied.

5. [ ] Unused labels with filled-in expiration date were destroyed.

6. [ ] Remaining labels, if any, were returned to proper storage area.

7. Place sample(s) of labels here:

8. Inspector ______________________  Completion date ______________________
   Comments: ______________________

9. [ ] Place completed form in the device history record for this lot.
   Form No. LC-11-21  Rev. A  Approved ______________________  Date ________
DEVICE HISTORY RECORD

I. INITIATION

DEVICE NAME: OB/GYN THEORETICAL YIELD: 2500
DEVICE LOT NO.: EXPIRATION:
INITIATED BY: DATE INITIATED:

II. FILLING OPERATIONS

A. CONTAINER: MFG: LOT NO.
B. LABELING

LABEL PREPARED BY:

LABEL APPROVED BY:

C. MEDIA

<table>
<thead>
<tr>
<th>SECTION</th>
<th>MEDIA</th>
<th>BATCH NO.</th>
<th>TEMP. RANGE</th>
<th>DEPTH OF FILL (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Levine EMB</td>
<td></td>
<td>41-52 C</td>
<td>3.5 - 4</td>
</tr>
<tr>
<td>2</td>
<td>Biggy</td>
<td></td>
<td>41-52 C</td>
<td>3.5 - 4</td>
</tr>
<tr>
<td>3</td>
<td>Mannitol Salt Agar</td>
<td></td>
<td>41-52 C</td>
<td>3.5 - 4</td>
</tr>
<tr>
<td>4</td>
<td>TSA w/5% Human Blood</td>
<td></td>
<td>44-52 C</td>
<td>3 - 3.5</td>
</tr>
<tr>
<td>5</td>
<td>Mod. Thayer Martin</td>
<td></td>
<td>44-52 C</td>
<td>2.5 - 3.5</td>
</tr>
</tbody>
</table>

FILLING ROOM PERSONNEL: 

DATE DEVICES FILLED: 

USER OR READER COMMENTS

In order to improve the quality and utility of our manuals and inserts, our company needs the active cooperation and participation of its user readership. Your comments as a user or reader will be greatly appreciated and reviewed for information in the next revision of this document.

Please comment on the completeness, accuracy, organization, usability, and readability of this manual or insert.

Did you find errors in this document? If so, specify by page.
How can this document be improved?

Other Comments:

User's Name:  Position:
Employer:  Department:
Address:
City:  State:
Zip:  Date:
Country:  Form Number: MKT-139 Rev. 1

Updated 1/1/1997
12. Product Evaluation

INTRODUCTION

Evaluation Specifications

CORRECTIVE AND PREVENTIVE ACTION

REPACKER/RELABELER DEVICE EVALUATION

NONCONFORMING PRODUCT

FAILURE INVESTIGATION

EXHIBITS

Portable Defibrillator Test Procedure
Test DHR of a Printed Circuit Board Assembly
Device History Record (urine plate)
Batch Production Record (XLD)
Batch Production Record (Thayer Martin)
Batch Production Record (Blank form)

INTRODUCTION

Product evaluation is performed to show with documented evidence that a component, in-process unit, or finished device was manufactured according to the device master record (DMR) and meets all of the acceptance criteria/acceptance specifications in the DMR. The blank forms for recording the data become a part of the DMR. The emphasis in this chapter is on finished device evaluation; however, evaluation of incoming product and in-process units is conducted according to the same type of controls [820.80(a), 820.80(b), 820.80(c)].

The GMP requirements for finished device evaluation are covered in section 820.80, which requires that the manufacturer establish and maintain procedures for finished device acceptance, to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. Finished devices shall be held in quarantine or otherwise adequately controlled until released. Finished devices shall not be released for distribution until:

- the activities required in the DMR are completed;
- the associated data and documentation is reviewed;
- the release is authorized by the signature of a designated individual(s); and
- the authorization is dated.
Manufacturers shall also identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of these items with acceptance criteria. The identification of acceptance status shall be maintained throughout manufacturing, packaging, labeling, installation, and servicing of the product to ensure that only products which have passed the required acceptance activities are distributed, used, or installed (820.86).

If a manufacturer has adequate test and inspection procedures and these are used correctly by appropriately trained personnel, then there is a high probability that devices released for distribution will meet the company device specifications for acceptable product. Further, the data collected during in-process or finished device evaluation should be appropriate, complete, and correct. This data shows the good and bad points about the product and specific production activities. The data may be fed back into the quality system to identify and solve real problems as well as to help maintain and improve the quality system.

**Evaluation Specifications**

In order to be assured that a device is fit for the intended use, a manufacturer should decide which characteristics of a device to test and/or inspect and to what detail or extent to test and/or inspect for conformance with the device specifications.

Decisions on what to test and how to test are made during the product and process development phase. For example, this decision is typically based on the:

- intended use;
- intended user;
- nature of the device and its components;
- intrinsic safety of the device;
- reliability of the device;
- overall process capability of the manufacturing operation;
- characteristics of test and inspection equipment and procedures; and
- performance margin of the device compared to the device specification.

Device test and/or inspection specifications, and test and/or inspection procedures, shall be carefully written and shall cover all appropriate points in the device acceptance specifications, in order to improve communication and reduce errors.

Design controls in 820.30(f) require device developers to verify the device design. Verification requires each manufacturer to write a test protocol and test, to the maximum feasible extent, all parameters of each device design against the design input specification. (The design input requirements become the input specifications at the verification stage of the development.) The verification test protocol includes the tests that will be performed on production units. Therefore, the production test procedures and some aspects of the inspection procedures are easily derived from the verification protocol.

Before the manufacturer is ready for full scale production, the test and inspection decisions shall be completed, documented as test/inspection or acceptance procedures, and approved for use. It is a violation of the FD&C Act to place inadequately evaluated devices into commercial distribution. It is also a violation of the quality system regulation to allow test and inspection procedures to evolve during production, except during a highly controlled
pilot-production phase. Further, devices that are not adequately evaluated may not meet company written or
unwritten quality claims -- manufacturers cannot bypass their responsibility by simply not writing quality claims.
Under Section 501(c) of the FD&C Act, a device is adulterated if its purity or quality falls below that which it
purports or is represented to possess.

By the time the manufacturer is ready for production, the device specifications shall be supported by one or more
test and inspection procedures documentation. These procedures are part of the DMR. To reduce drafting, filing,
retrieval, and copying costs, test and inspection procedures may appear on process and assembly documents.
Combination documents are commonly used for the fabrication and inspection/testing of subassemblies. There
may be several test and inspection documents because evaluation may be performed at several in-process stages
and at the finished device stage.

Although the manufacturer shall establish and maintain procedures for finished device acceptance, there are
situations where a simple data sheet or blueprint may be referred to as the written acceptance criteria. For
example, the acceptance of a simple molded or machined component or device may be determined by using a
checklist, blueprint, or specification which specifies finished article dimensions, flash removal, etc. In machine-
shop operations, a blueprint or engineering drawing may be used as acceptance criteria and used to meet the
quality system written procedure requirements.

CORRECTIVE AND PREVENTIVE ACTION

GMP section 820.100 requires an analysis of problem data, returned product, and an investigation of non-
conforming product. Also 820.198 requires an investigation of complaints that allege a device does not meet
specifications. Section 820.100 refers to analysis of processes, work operations, concessions, quality audit
reports, quality records, service records, complaints, returned product, and other sources of quality data to
identify existing and potential causes of nonconforming or other quality problems. Section 820.198 also involves
reviewing and evaluating complaints to determine whether or not an investigation is necessary. All these
activities and their results shall be documented.

Some devices have a specified requirement for servicing. If this is the case, the manufacturer shall establish and
maintain instructions and procedures for performing and verifying this servicing (820.200). The servicing reports
shall also be analyzed using 820.100, Corrective and Preventive Action; if the servicing involves a death or
serious injury, the service report is considered to be a complaint per section 820.198, Complaint Files, and is
reported to FDA per parts 803 and 804, Medical Device Reporting.

The significance of the device and any hazard the defective device presents should be taken into consideration
when determining compliance with corrective and preventive action requirements. Analysis shall be taken to the
level necessary to determine the actual failure mechanism, e.g., defective component, incorrect raw material,
erosion, composition, etc. The cause of failure is obvious in some cases and a formal investigation may not be
needed. A record of the investigation, follow up, and conclusions shall be made in accordance with section
820.100.

When a systematic failure has been diagnosed, manufacturers need not analyze every device with the same
diagnosed symptoms. However, enough devices should be analyzed to clearly establish symptoms before any
assumptions are made about the cause of failure or about corrective actions. When an investigation results in
identification of a deficiency, such as a failed component or a design flaw, and this deficiency may exist in other
product lines, the investigation will not be effective unless it extends to determining the effect on other product lines.

If the failure is design related, the design shall be corrected per the design control requirements in 820.30 in order for the devices to meet company quality claims and not be adulterated under the FD&C Act section 501(c). When a failure is determined to be related to documentation, assembly, processing, labeling, testing, packaging, or other manufacturing operations, the manufacturing deficiency shall be identified, corrected, and documented.

**REPACKER/RELABELER DEVICE EVALUATION**

Finished devices received by a repacker/relabeler typically have been inspected and conform to specifications determined by the original manufacturer except for the final packaging and/or labeling. In most cases a repacker/relabeler would not have to assure that the finished device as received meets performance and configuration specifications. Finished bulk materials, such as dental resins, in vitro diagnostics, etc. may be accepted on the basis of a certificate of analysis for each batch.

Before releasing devices for distribution, repackers/relabelers should assure that devices are properly labeled (see chapter 11) and packaged (integrity, contents, etc., also see chapter 13). Often this can be accomplished using a list, illustration, or a model. When the packaged product will be sterilized or aseptically filled, written instructions and inspection/testing are necessary. Final acceptance of repacked/relabeled devices shall be recorded in accordance with 820.80(e). As noted, the final acceptance data is primarily related to correct labeling, correct packaging, and sealing of the packaging. In the case of aseptic filling operations, validation of the filling operations and finished device sterility testing are required.

**NONCONFORMING PRODUCT**

The manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. These established procedures shall include identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of product non-conformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. This evaluation and any investigation shall be documented (820.90). The manufacturer shall establish procedures for identifying the training needs of personnel who handle nonconforming products in the course of their work. These people should be trained to recognize product noncomformance and take appropriate action to control nonconforming products including identifying product as nonconforming, documenting and evaluating the nonconformance, and segregating and disposing of nonconforming product. This training should be documented (820.25).

To facilitate detection of failure or defect trends, internal problem data, including service reports, and complaints should be arranged in a way that permits correlating present and past data for a particular product or product line. This can usually be achieved by organizing files according to product or product lines. Such data may be maintained in a computer file for quick accessibility and analysis.

The manufacturer shall establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product. Nonconformance may occur in-house, as well as before product is distributed, along with nonconformances of distributed product. Procedures shall set forth the review and disposition process. Disposition of nonconforming product shall be documented. This documentation shall
include the justification for any use of nonconforming product and the signature of individual(s) authorizing this use [820.90(b)(1)]. The decision to use a nonconforming product is usually done by a material review board (MRB). MRB boards should operate according to a written procedure and be comprised of individuals having the knowledge to determine suitability for use of nonconforming product.

Each manufacturer shall establish and maintain procedures for rework, including retesting and reevaluation of the nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including the determination of any adverse effects from the product rework, shall be documented in the DHR [820.90(b)(2)].

**FAILURE INVESTIGATION**

In order for a quality system to be self correcting, data on quality problems from all sources should be fed back into the system. For example, complaints, service reports, and nonconforming products can provide valuable information that can point toward possible corrective actions. The more comprehensive a quality system is in taking preventive action, the lower the probability of customer dissatisfaction and the resulting need for corrective action. A true quality system has many preventive safeguards including GMP requirements for design, packaging, labeling, manufacturing control, installation, repairs, and complaint and failure analysis. A quality system that also covers the customer needs generally results in increased overall quality and greater customer satisfaction.

Service requests resulting from long use, misuse or accidental damage usually do not require corrective and/or preventive action. However, if service requests or other customer concerns are the result of rapid wear, unusual problems, unusual maintenance, or development of hazardous conditions, action may be necessary.

The manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include the following [820.100(a)]:

- Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data. The purpose of the analysis is to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.

- Investigating the cause(s) of nonconformities relating to product, processes, and the quality system.

- Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems.

- Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.

- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.

- Ensuring that information related to quality problems or nonconforming product is disseminated to those
directly responsible for assuring the quality of such product or the prevention of such problems.

- Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

All these activities and their results shall be documented [820.100(b)].

**EXHIBITS**

Several forms for recording device production and evaluation data are briefly described below and then exhibited.

**Portable Defibrillator Test Procedure**

Ten pages extracted from a 31-page test specification for a family of portable defibrillators are reprinted below. This test procedure is long and detailed because a defibrillator is a complex device with a benefit to risk ratio that approaches infinity. This sample evaluation procedure covers final manufacturing, testing, and data collection performed by the production department to make absolutely certain that finished defibrillators comply with DMR specifications. This test procedure was developed based on the company approved device specifications.

To reduce errors and increase clarity, the test number column on the data sheet contains the paragraph number of the detailed requirements in the specifications section of the procedure. The test equipment and schematics are not reprinted here.

**Test DHR of a Printed Circuit Board Assembly**

A data or "device history record" card for a printed circuit board is exhibited. The test procedure for the board is not reprinted. This data card is not the complete device history record for the finished device. When the finished device is tested, this board is tested again as an integral part of it.

**Device History Record (urine plate)**

A record sheet of the filling, labeling sample, inspection, and sample testing of a five-media urine plate is exhibited. Each activity is performed per procedure -- these procedures are not exhibited. The label record is an actual label as printed on the urine plates -- the record sheet is passed through the printing machine. This technique reduces costs and eliminates human copying errors.

**Batch Production Record (XLD)**

This exhibit is the batch production record of the XLD component used to fill one section of the five-part urine plate discussed above.

**Batch Production Record (Thayer Martin)**

This exhibit is a blank copy of the form used to record the batch production record for the Thayer Martin
component used in the urine plate.

**Batch Production Record (Blank form)**

This exhibit is a form used to record the batch production record of various growth media. It could be used to record the production of XLD as mentioned above.
1.0 **OBJECT:**

To test the D-320, D-320W, D-400 or D-400W Portable Defibrillators for conformance to Engineering Specifications and to define the equipment and methods to perform these tests.

2.0 **METHOD:**

The Portable Defibrillator will be subjected to the following test sequence:

1. **PC Boards Test**
   1. Preliminary Test/Display Adjustments
   2. Burn-In
   3. Final Checks
2. **Writer Tests**
   1. Preliminary Tests
   2. Burn-In
   3. Final Tests
3. **Final Tests**
4. **Battery Operation**
5. **Safety Tests**

3. **EQUIPMENT:**

1. Scope, Tektronix Type 5103 or equivalent (DUAL TRACE SCOPE).
2. DVM, Fluke Type 8000A or equivalent.
3. Test Set #2033 (Ed. Test Set).
4. Heart Simulator, HS-1 or equivalent.
5. Function Generator, Krohn-Hite Type 5300 or equivalent.
6. Frequency Counter, HP Type 5512A or equivalent.
7. Noise Meter, HP Type 403 or equivalent.
8. Power Monitor, Soncorpe Type PM-157 or equivalent.
9. Variac, Power Stat Type 116 or equivalent.
10. Defibrillator Meter, Dempsey Type 429 or equivalent.
11. Pretested Adult Anterior Paddles (P/N 2499008201).
12. Electronic Stop Watch.
13. Pretested Scope Board, Defibrillator Board, Heart Rate Board, ECG Board and, if required, Writer Board.
14. Test Set #2030 (Stat Scope Test Set).
15. Test Plug #2036 (Int. Pad/Remote Chg.).
16. Adapter #2037 (Paddle Conn.).
17. Test Set #2041 (Writer Test Set).
4. DRAWINGS:

1. Prod./Test Spec., Portable Defibrillator A94300538
2. Schematic, Portable Defibrillator A04300211
3. Schematic, Scope Board C04300602

5. Schematic, Defibrillator Board D04300207
6. P.W. Assy., Defibrillator Board E20300207
7. Schematic, Heart Rate Board C04300617
8. P.W. Assy., Heart Rate Board E20300617
9. Schematic, ECG Board D04300209
10. P.W. Assy., ECG Board E20300209
11. Schematic, Writer Board C04500230
12. P.W. Assy., Writer Board C20300210
13. Schematic, Test Load Board D04300618
14. Assy., Test Load Board C20300618
15. QA Policy and Procedure, Section No. 26 (Elevated temperature burn-in of products).
17. Test Procedure, Systems Safety A05000009

5.0 PROCEDURE:

NOTES: (1) WHEN TESTING THE D-320/400, HIGH VOLTAGES AND HIGH ENERGY LEVELS ARE PRESENT ON THE P.C. BOARDS AND CHASSIS MOUNTED COMPONENTS, ALL NECESSARY SAFETY PRECAUTIONS SHOULD BE TAKEN.

(2) The Printed Circuit Boards will be tested as a complete assembly, burned-in, re-tested, assembled into the main chassis (by production) and final tested as a complete portable defibrillator.

(3) Use an insulated blade screwdriver for making all the portable defibrillator adjustments.

(4) See APPENDIX 1 for the physical location of the pots and test points on the portable defibrillator.

(5) The Writer will be tested as a separate assembly, burned-in, re-tested and assembled into the D-320W/400W.
5.1.1 PRELIMINARY TESTS/POWER CONSUMPTION

5.1.1.1 Connect the P.C. Board assemblies into Test Set #2033, insuring the P.C. Boards slide into the P.C. guides. Connect the CRT connector on the Scope Board to the CRT and connect the two ribbon cables (P2 and P3) on the Test Set and P4 to the appropriate jacks on the DEFIBRILLATOR board. Connect the red clip lead to TP-12 on the defibrillator board.

5.1.1.2 CONNECT A JUMPER BETWEEN E3 AND E4 ON THE DEFIBRILLATOR BOARD AND CONNECT E4 TO GREEN WIRE GROUND.

5.1.1.3 Depress 1 pushbutton and release the remaining pushbuttons on the P.C. Boards. Rotate the high alarm control CW and the low alarm control CCW.

5.1.1.4 Connect the Scope to TP-10 on the SCOPE Board. Set the MAIN POWER switch on the test set ON. Depress the POWER ON pushbutton on the Test Set. The Scope should display a 15-20Vpp, 18-22 KHz square wave within 1/2 second of turning on, with rise and fall times < 3.5ms. Two traces should be visible on the CRT within 15 seconds from the time power was applied to the unit.

5.1.1.5 Connect the DVM (DCV) between TP-19 (GND 1) and TP-9 (+10V) on the SCOPE Board. The DVM should read 9.8 ± 0.1V. Disconnect the DVM from the SCOPE Board.

5.1.1.6 Adjust the INTENSITY pot (R64) on the SCOPE Board to just below the point where the traces begin to unblank.

5.1.1.7 Adjust the "V" ROT. pot (R89) on the SCOPE Board for a horizontal trace parallel to the bottom of the CRT.

5.1.1.8 Connect the HR simulator to the ECG board patient connector (simulator power off). Rapidly depress the HV pushbutton on the B-320/400. Adjust the SIZE control for ≥ 4 cm deflection.

5.1.1.9 When the HV pulses fill the screen horizontally, depress the FREEZE pushbutton on the HEART RATE Board. The HV pulses should "Freeze".

5.1.1.10 Adjust the FOCUS pot (R73) and the ASTIG pot (R60) on the SCOPE Board for the sharpest trace at the center of the display.
5.1.1.11 Adjust the "X" POT, pot (R122) on the Scope Board until the MV pulses are parallel to the sides of the CRT.

5.1.1.12 Adjust the VERTICAL POSITION pot (R86) on the SCOPE Board so that the HR bar is ± 1/2 cm from the bottom of the CRT.

5.1.1.13 Adjust the HORIZONTAL POSITION pot (R92) on the SCOPE Board so that the HR pointer is at the left edge of the CRT.

5.1.1.14 Adjust the SWEEP RATE pot (R78) on the SCOPE Board so the right edge of the traces are at the right edge of the CRT.

5.1.1.15 Release the FREEZE button. The MV pulses should unfreeze.

5.1.1.16 Depress the RECORD pushbutton on the HR Board. The RECORD lamp on the Test Set should be on. Release the RECORD button. The RECORD lamp should be off.

5.1.1.17 Adjust the Heart Rate Simulator for ≈ 120 BPM. The D-320/400 should display the ECG complex. Rotate the HIGH limit control on the Heart Rate Board fully CCW. Within three seconds after the heart rate pointer goes above the high alarm limit on the HR bar, the following alarm conditions should exist: (1) Steady audio tone, (2) The ALARM light on the HEART RATE Board should be flashing at ≈ 2HZ rate and (3) RECORD lamp on the Test Set on. Rotate the HIGH alarm limit fully CW. The alarm conditions should cease.

5.1.1.18 Rotate the LOW limit fully CCW. Within three seconds after the limit passes the HR pointer, the previous alarm conditions should exist. Rotate the LOW limit fully CW. The alarm conditions should cease.

5.1.1.19 With the DVM on DC volts, measure the voltage at the POWER IN side of F2 on the DEFIBRILLATOR Board. Note the value.

5.1.1.20 Set the MAIN POWER on the Test Set OFF. Remove F2.
5.1.1.20 Set the MAIN POWER on the Test Set OFF. Remove F2 from the fuse holder and connect the DVM (2000 mADC range) across the fuse holder.

5.1.1.21 Set the MAIN POWER on the Test Set ON. The DVM should read within the voltage/current limits specified in the following table at the voltage measured in step 5.1.1.19:

<table>
<thead>
<tr>
<th>Voltage (V)</th>
<th>12V</th>
<th>13V</th>
<th>14V</th>
<th>15V</th>
<th>16V</th>
<th>17V</th>
<th>18V</th>
<th>19V</th>
<th>20V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current (mA)</td>
<td>332</td>
<td>298</td>
<td>277</td>
<td>259</td>
<td>243</td>
<td>228</td>
<td>216</td>
<td>204</td>
<td>194</td>
</tr>
</tbody>
</table>

5.1.1.22 Set the MAIN POWER on the Test Set OFF. Disconnect the DVM from the fuse holder and insert the 0.5A fuse.

5.1.1.23 Set the Test Set main power switch ON. Momentarily depress the MAN, CHG. pushbutton on the Test Set. The DRY-LED on the test set should come on and the HR bar should be blinking. Rotate the CHG. pot on the Test Set slowly CCW. The defibrillator bar should appear at the top of the CRT flashing alternately with the HR bar and increasing in length as the CHG. pot is rotated. Adjust the defib bar for full screen width. When the MAN button is depressed, a momentary audio tone should be present indicating the defib. is charging.

5.4.2 CHARGING CURRENT/BATTERY DRAIN/CHARGE TIME

5.4.2.1 Connect the (-) battery terminal to E2 on the defibrillator board. Connect the DVM (200mADC) in series with E1 on the defibrillator board and the (+) terminal of the battery. Connect the line cord to AC power.

5.4.2.2 The DVM should read 150±30mA. Set the DVM to the 2000mA range.

5.4.2.3 Disconnect the line cord from AC power and depress the D-320/400 POWER ON button. The DVM should read 300mA.
5.4.2.3 Disconnect the line cord from AC power and depress the D-320/400 POWER ON button. The DVM should read 300mA.

5.4.2.4 D-320W/400W only depress the RECORD button. The DVM should read 1000mA. Release the RECORD button.

5.4.2.5 Depress the POWER OFF button, disconnect the DVM from the D-320/400 and disconnect all other test equipment and cables from the D-320/400. Reconnect the (+) battery lead to F1 on the defibrillator board.

5.4.2.6 Connect the D-320/400 to AC power and charge the battery for 14 hours minimum.

5.4.3 BATTERY LIFE

5.4.3.1 Depress the POWER ON button.

5.4.3.2 Depress the FREEZE button and then disconnect AC power from the D-320/400. There should not be any changes in any of the traces (no "dropped bits", noise, etc.). Release the FREEZE switch.

5.4.3.3 Operate the D-320/400 on battery operation. The LOW BATTERY indicator should be off. Every 30 minutes check the D-320/400 for a LOW BATTERY indication. Note the time LOW BATTERY comes on.

5.4.3.4 Check the operation of the D-320/400 every 15 minutes after LOW BATTERY comes on and note the time it stopped operating. This time should be 5 hours from the start of the test and 0.5 hours from the start of a LOW BATTERY indication.

5.4.3.5 Depress the POWER OFF button and disconnect the RR SIMULATOR.

5.5 SAFETY CHECKS

5.5.1 Using Test Procedure A05000009, perform the following Safety Tests:

5.5.1.1 AC HI-POT (PRIMARY POWER - 2500VAC for 1 minute).
3.5.1.2 AC HI-POT (ISOLATED INPUT - 2500VAC for 1 minute).
3.5.1.3 Isolation (BKvDC from either paddle to ground - HV relay energized).
3.5.1.4 RISK CURRENT (10mA @ 120V/60Hz)
3.5.1.5 GREEN WIRE LEAKAGE (300mA RMS)

5.5.2 After safety checks are completed, connect the heart simulator to the D-320/400 and insure the following are operating correctly:

1. ECG complex on screen and size control varies amplitude.
2. ECG complex in Lead I, II, III and beep O.K.
3. Connect test set and check INT and EXT HV.
4. Freeze OK.
5. HR BAR indicates rate
6. HI/LO alarms operable and writer writes out during alarm conditions.
7. Any auto or man charge turns off writer (unless writer was manually started).
9. Man/auto 160 (200)/auto 320 (400) OK
10. In sync mode, sync pulse on peak to trailing edge of "R" wave.
11. Man (paddles) discharge OK.
12. In sync, defib only discharges when "R" wave detected.
13. Auto (45 second) timeout OK.
14. Disarm OK
### D-320(W)/400(W) Data Sheet

**Test Function** | **Data** | **Comments** | **Accept** | **Reject**
--- | --- | --- | --- | ---
5.1.1 Preliminary Tests/Power Consumption | V mA | See Table - Step 5.1.1.21 | | |
5.1.2 P.C. Boards - Burn-In | Hrs | 96 Hours Minimum @ 55°C | | |
5.1.3 P.C. Boards - Final Checks | | | | |
5.3.1 Resistance Checks | Ω | ≤ 0.01Ω (Ground) | | |
5.3.2 Power Supply Check/Preliminary Checks | V | 9.8±0.1V | | |
5.3.3 ECG Transient Response | | <5% of the 1MV pulse | | |
5.3.4 ECG Amp - Output Offset | mV | 0±10mV | | |
5.3.5 ECG Amp Gain/Display Gain/Writer Gain | Vpp(ECG) Cmpp(DIS) Cmpp(WR) Vpp(ECG) Cmpp(DIS) Cmpp(WR) | 1.0+0.0, -0.2Vpp MIN. 1.0+0.0, -0.1Cmpp MAX. | | |
5.3.6 ECG Notch Filter Adjustments | mVpp | | REF. | |
<table>
<thead>
<tr>
<th>TEST NO.</th>
<th>TEST FUNCTION</th>
<th>DATA</th>
<th>COMMENTS</th>
<th>ACCEPT</th>
<th>REJECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3.7</td>
<td>ECG/Display/</td>
<td>Vpp(ECC) 0.71-1.0 @ 0.5Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Write Frequency</td>
<td>cmpp(DIS.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Response</td>
<td>cmpp(WR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vpp(ECC) 0.71-1.0 @ 40Hz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cmpp(DIS.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cmpp(WR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.8</td>
<td>ECG Reset Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.9</td>
<td>ECG 1MV CAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.10</td>
<td>ECG/Display/</td>
<td>mV &lt; 5μV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Short Circuit Noise</td>
<td>cmpp &lt; 0.5μmpp</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.11</td>
<td>ECG Output</td>
<td>Vpp</td>
<td>Lead I 1.0Vpp</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frujarity/Lead</td>
<td>Vpk</td>
<td>Lead II</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Selector</td>
<td>Vpk</td>
<td>Lead III 1.0±0.2Vpk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vpk</td>
<td>Paddles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.12</td>
<td>Heart Rate Cal./</td>
<td>Bpm</td>
<td>240 BPM REF.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Accuracy</td>
<td></td>
<td>120±6 BPM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.13</td>
<td>Heart Rate/</td>
<td>Vpk</td>
<td>≤ 0.3cmpp</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symp Threshold</td>
<td>Vpk</td>
<td>≤ -0.3cmpp</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.14</td>
<td>Heart Rate</td>
<td>BPM</td>
<td>HI 50-250 Min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HI/Lo Alarm</td>
<td>BPM</td>
<td>LO 0-120 Min.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.15</td>
<td>Heart Rate Pacer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Artifact Rejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.3.16</td>
<td>Defibrillator Energy</td>
<td>j</td>
<td>160(200) J, REF. j</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level Adjust</td>
<td>320±6.4 j (400±8j)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table

<table>
<thead>
<tr>
<th>Test No.</th>
<th>Test Function</th>
<th>Data</th>
<th>Comments</th>
<th>Accept/Reject</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.3.22</td>
<td>Defibrillator Remote Chg./ Int. Paddle Discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4.1</td>
<td>Low Battery Adj./ Charge Time</td>
<td></td>
<td>Set at 12.30 VDC</td>
<td></td>
</tr>
<tr>
<td>5.4.2</td>
<td>Charging Current/ Battery Drain</td>
<td>mA</td>
<td>150±30mA, 130 (300 mA)</td>
<td></td>
</tr>
<tr>
<td>5.4.3</td>
<td>Battery Life *</td>
<td>RMS</td>
<td>&gt; 5 Hours with ECG Signal Only</td>
<td></td>
</tr>
<tr>
<td>5.5.1.1</td>
<td>AC HI-Pot (Primary Power)</td>
<td></td>
<td>2500VAC for One Minute</td>
<td></td>
</tr>
<tr>
<td>5.5.1.2</td>
<td>AC HI-Pot (Isolated Input)</td>
<td></td>
<td>2500 VAC for One Minute</td>
<td></td>
</tr>
<tr>
<td>Regulation</td>
<td></td>
<td></td>
<td>8 kVDC from</td>
<td></td>
</tr>
<tr>
<td>Specification</td>
<td>Test Methodology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5.1.3</td>
<td>8KVDC from paddles to ground</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5.1.4</td>
<td>Risk Current, µA ≤ 10µA @ 120V/60HZ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.5.1.5</td>
<td>Green Wire Leakage, µA ≤ 50µA RMS @ 120V 50/60HZ</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*OPTIONAL*

**FINAL ACCEPTANCE**

**DATE**

**REVIEWED BY**

**DATE**

**REV.**

**05000045**

**SHT 24**

---

Sample: Electrical Inspection and Test DHR
Of A Printed Circuit Board Assembly
This history record is used with a written test procedure (not shown). The test procedure includes the allowed range of values for each parameter.

NOTE: Reverse side of card is used to record rework in comment form.

Rework Record

By

etc

12-18
Device History Record

I. INITIATION

Device Name: Urine Plate  
Device Lot Number: 05 1541  
Theoretical Yield: 1538  
Expiration: 7-24-84

II. FILLING ROOM OPERATIONS

A. Container Size:  
Mfg.  
Mfg. Lot Number: 4680679-3

B. COMPONENTS  
<table>
<thead>
<tr>
<th>BATCH NO.</th>
<th>FILLING RANGE</th>
<th>VOLUME OF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lowine EMB</td>
<td>6234</td>
<td>46 - 48 C</td>
</tr>
<tr>
<td>2. XLD</td>
<td>6236</td>
<td>46 - 50 C</td>
</tr>
<tr>
<td>4. TSA 5K</td>
<td>6233</td>
<td>46 - 48 C</td>
</tr>
</tbody>
</table>

Personnel in Room: DVC + SGC  
Actual Yield: 1501

Date Filled: 5/16/84

SECTION APPROVED BY: DVC  
DATE: 5/16

III. LABELING OPERATION

A. Date Prepared: 5/17

SECTION APPROVED BY: DVC  
DATE: 5/17

B. Plate Inspection:
- CONTAMINATED: 0
- SPILLOVERS: 26
- UNEQUAL FILLS: 2
- MISHANDLED: 0
- OTHER: 0
- TOTAL REJECTED: 27
- TOTAL NO. ACCEPTED: 1450

C. Insert Control:
Number of Inserts: 146

IV. QUALITY CONTROL

STERILITY SAMPLES SUBMITTED ON 5/16
PERFORMANCE SAMPLES SUBMITTED ON 5/16

1450 Released  27 Rejected

Device Released For Distribution By: 5/22/84  
Date: 5/19
Batch Production Record

I. PREPARATION

Component Name: XLD
Batch Production No.: 6236

Number of Flasks: 4
Flask Size: 3.5 L

Her Number of Flasks in Total Batch: 4

<table>
<thead>
<tr>
<th>INGREDIENT</th>
<th>INGR. MFG.</th>
<th>MFG. LOT NO.</th>
<th>AMT. PER FLASK</th>
</tr>
</thead>
<tbody>
<tr>
<td>XLD</td>
<td>BRL</td>
<td>XXX</td>
<td>123.45</td>
</tr>
<tr>
<td>deionized water</td>
<td></td>
<td></td>
<td>3.5 L</td>
</tr>
</tbody>
</table>

II. STERILIZATION & MEDIUM COOLING

<table>
<thead>
<tr>
<th>AUToclave NO.</th>
<th>CYCLE TIME &amp; TEMP</th>
<th>TIME IN</th>
<th>START</th>
<th>STOP</th>
<th>TIME OUT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Boiled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Water Bath Temperature: 35 to 48

III. DEVICES FILLED

<table>
<thead>
<tr>
<th>LOT NUMBER</th>
<th>VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>061541</td>
<td>14 L</td>
</tr>
</tbody>
</table>
IV QUALITY ASSURANCE

Approved             Rejected

Batch Released By: 12-20

DATE: 5/27

I. PREPARATION

MEDIA NAME: Mod. Thayer Martin

BATCH PRODUCTION NO.:__________

TYPE OF VESSEL: Bulk Solution Sterilizer

VESSEL NO:__________

INGREDIENT          INGREDIENT          MFG. LOT QUANTITY
                    MFG.               NO.            

G.C. Agar Base      __________  __________  1.800 kg.
Bact. Agar          __________  __________  g.
Deionized water     __________  __________  32.0 liters

PREPARED BY:__________

II. STERILIZATION

STERILIZATION CYCLE AND TEMP.: 15 MINUTES AT 121 C

TIME STEAM ENTERS JACKET:__________

TIME STERILITY CYCLE BEGAN:__________

TIME STERILITY CYCLE COMPLETED:__________

TIME VESSEL REACHES DISPENSING TEMP.:__________
TIME VESSEL REACHES DISPENSING TEMP.: __________

STERILIZATION CYCLE MONITORED BY: __________

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>BATCH NO.</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choc. Enrich. Sol.</td>
<td>_________</td>
<td>500 ml.</td>
</tr>
<tr>
<td>VCA+ T Sol.</td>
<td>_________</td>
<td>357 ml.</td>
</tr>
<tr>
<td>Hemoglobin Sol.</td>
<td>_________</td>
<td>10 liters</td>
</tr>
</tbody>
</table>

ADDED BY: __________

<table>
<thead>
<tr>
<th>DEVICE LOT. NO.</th>
<th>VOLUME</th>
</tr>
</thead>
<tbody>
<tr>
<td>1._________</td>
<td>_____</td>
</tr>
<tr>
<td>2._________</td>
<td>_____</td>
</tr>
</tbody>
</table>

IV. QUALITY ASSURANCE

APPROVED _____ REJECTED _____ DATE _______ BY _______

12-21

BATCH PRODUCTION RECORD

<table>
<thead>
<tr>
<th>MEDIUM NAME</th>
<th>BATCH NUMBER</th>
<th>MASTER SHEET</th>
<th>BY</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMPONENT DESCRIPTION</th>
<th>UNITS</th>
<th>LOT NO.</th>
<th>TOTAL AMT</th>
<th>AMOUNT</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Sterilization

<table>
<thead>
<tr>
<th>Autoclave No</th>
<th>Cycle Time</th>
<th>Time In</th>
<th>Start</th>
<th>End</th>
<th>Time Out</th>
<th>Remarks</th>
<th>Date</th>
</tr>
</thead>
</table>

### Medium Cooling

<table>
<thead>
<tr>
<th>Water Bath Temp</th>
<th>By</th>
<th>Remarks</th>
</tr>
</thead>
</table>

### Lots Filled

<table>
<thead>
<tr>
<th>Lot Number</th>
<th>By</th>
<th>Date</th>
</tr>
</thead>
</table>

### Equipment & Container Cleaning

<table>
<thead>
<tr>
<th>Cleared By</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Inspected By</th>
<th>Date</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Removed By</th>
<th>PM</th>
<th>Date</th>
</tr>
</thead>
</table>

Updated 1/1/1997
13. Packaging

INTRODUCTION

PACKAGING DESIGN CONTROLS
User Preference

PACKAGING MATERIALS

PACKAGE VALIDATION

PROCUREMENT, ACCEPTANCE, AND STORAGE

PACKAGING PROCESS

exhibits
Product Specification: Pouch
Header Bag (Specification Form)

INTRODUCTION

The packaging industry is continuously evolving as medical product companies institute changes in the design, development, and manufacture of packaging systems. Thus, this chapter is not aimed at providing an all-inclusive list of packaging procedures and/or materials. Rather the goal is to instill an awareness of important packaging issues involving both design and manufacture. This chapter will also provide a basic understanding of the importance of validating processes and equipment, and the continuing need to maintain control of established packaging processes. The result should be a package that protects the device during handling and shipping, and from the environment and microorganisms until the package is opened. This includes allowing for any necessary sterilization. Packaging contains the product identification and other information as described in Chapter 11, Labeling. Packaging may also contain integral labeling and instructions for use or these instructions may be in a manual or package insert. Finally, when the consumer is ready to use this product, the package should be easy to open without compromising the quality of the device. In the end, a well designed package facilitates use of the device and contributes substantially to the overall appeal of the product. It makes sense for the manufacturer to invest in the development of a safe, user friendly package.

The design of the device, the labeling, the packaging and the manufacturing processes form the design output [820.3 (g)]. These should be integrated. Manufacturers should consider the needs of the user as required by 820.30, Design Controls. Manufacturers should document these design outputs in the device master record then, procure, handle, store, and use the specified materials according to the device master record. FDA regulations are compatible with this total systems approach to device process design, production, packaging, and labeling.
Finally, manufacturers should perform quality assurance tests or acceptance tests on samples of the finished packages and, if sterilized, repeat the tests after sterilization. These tests should be based on a statistically valid sample to insure confidence that the packaging is capable of maintaining the integrity of the finished product. Where the device is very expensive, or only available in small quantities, the packaging tests may be performed on labeled, controlled packages that contain identified, rejected or simulated devices, as appropriate. The results of testing and/or inspection should be recorded in the device history record. Correctly performing these activities can reduce or prevent customer complaints, recalls, and product liability actions.

PACKAGING DESIGN CONTROLS

Package design should be an integral part of the product development program. Waiting until the end of the development process to design packaging can result in severe delays in getting the product into distribution. The whole idea is to "build quality in." The total device and package system should be considered with respect to: device characteristics, sterilization process if any, sealing, labeling, secondary packaging, handling, shipping, environment, storage, federal regulations, and end use.

Defective packaging and seals have been a major cause of medical device recalls. This type of recall can often be avoided by correct package design including validation of the packaging and sealing processes. Packaging and sealing machines should be set up according to written procedures that are based on the known capability of the manufacturing system. It is important to be aware of the state-of-the-art in sealing methods and packaging materials, including their physical, chemical, biological, and compatibility characteristics and, of course, cost. "Wet" devices require high-barrier package materials and sealants with impermeability; resistance to solvents, grease, chemicals, and heat; and the ability to contain wetting agents, reagents, oils, or fragrances. Thus, the ability to seal in the presence of liquid components, if spillage occurs in the seal area, is important. Some peelable adhesives are highly solvent-resistant and also remain intact during radiation sterilization. If necessary, obtain guidance from suppliers, technical literature, and consultants. After the process has been developed and validated, the packaging aspect of production should be performed according to GMP requirements in order to maintain a state of control.

The design controls established by 21 CFR 820.30 and, particularly 820.3(g), define packaging as part of the device design output. This means the design phase of packaging shall include the application of quality systems requirements and the documentation of these applications. Control over package design shall be performed according to 820.30 for any Class II or Class III devices, devices automated with computer software, and the following Class I devices:

<table>
<thead>
<tr>
<th>Device</th>
<th>Section</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter, Tracheobronchial Suction</td>
<td>868.6810</td>
</tr>
<tr>
<td>Glove, surgeon's</td>
<td>878.4460</td>
</tr>
<tr>
<td>Restraint, Protective</td>
<td>880.6760</td>
</tr>
<tr>
<td>System, Applicator, Radionuclide, Manual</td>
<td>892.5650</td>
</tr>
<tr>
<td>Source, Radionuclide Teletherapy</td>
<td>892.5740</td>
</tr>
</tbody>
</table>

Manufacturers of other Class I devices should establish and maintain procedures for ensuring that their device design is correctly translated into production specifications. They may use 820.30(h) as guidance. For these Class I devices that require design controls, packaging design is performed according to 820.130. The nature of the device as well as the sterilization method(s), intended use, shelf life, transport, and storage all affect package design.
The following activities are important to maintain control of package design:

1. Planning for the design and development of packaging; and defining responsibility for implementation of design activities and controls. These plans should identify the different groups and activities providing input into the design process. Periodic review and approval is necessary as the package design evolves.

2. Establishing design input and output procedures, including review, documentation, signature, and date, that are appropriate for the intended use and the needs of the user and the patient. The procedures shall include safeguards for addressing concerns about the proposed designs.

3. Ensuring that design review procedures for all appropriate stages of the design development are conducted by qualified individual(s) and include an individual not directly responsible (NDR) for the design stage under review. This NDR person could be one of several people on the design review committee. The design identification, review results, reviewers, and date shall be documented in the design history file [820.30(j)].

4. Documenting design verification/validation to confirm that the design output meets the design input requirements in the design history file. This documentation must include the reviewers and date of review.

5. Establishing and maintaining design transfer procedures that insure that the package design is correctly translated into production specifications. The correct translation, of course, may be directly done as part of the design output.

6. After the package design is accepted, controlling changes according to company change control procedures. The manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation. A significant part of this control is achieved when design controls are followed.

7. Establishing a design history file to demonstrate the design was developed and approved according to plan. This, of course, should show that the design output meets the design input -- a fact which should be obvious from data presented during the final design reviews.

Design controls require that a packaging design undergo considerable validation, review, and documentation. However, the end result is a smooth transfer into production with increased package safety and efficacy, resulting in greater customer satisfaction and cost savings and reduced liability.

In addition to the GMP requirements, manufacturers should always study current packaging practices for products similar to theirs to determine current favorable practices and to prevent user packaging problems. For example, customary use may dictate the use of double primary packaging for some sterile devices. Finally, any packaging used for medical devices should satisfy the end user or customer requirements, which automatically satisfies one of the design GMP requirements. This is a key point to be considered during the design phase.

User Preference

In the Medical Device and Diagnostic Industry magazine, the article, "Hospital-User Preference in Sterile Device Packaging," reports the results of a survey of nurses from operating room and central services areas of hospitals. Several conclusions from the test results are listed below that should be of interest to sterile device manufacturers.
96 percent of the nurses had become "increasingly aware of the importance of quality packaging to infection control."

90 percent said that packaging quality could influence their selection of a sterile medical device.

87 percent wanted at least one package side to be transparent.

95 percent preferred the adhesive to transfer from the lid to the lip of a tray when opened to indicate a broken seal.

89 percent wanted sterilization process indicators printed on packages for sterile devices.

99 percent said fiber-free opening of a sterile device package is important or very important.

55 percent believed larger, high-profile devices would be best packaged in a tray with a peelable lid.

55 percent preferred black printing on the package for easy reading.

Package features that might favorably influence practitioners in the selection of a sterile medical device include:

- clean, fiber-free opening,
- double packaging,
- printed process indicator,
- easy-open notches on chevron peel pouches, and
- lids with adhesive transfer.

The nurses believe that being able to see and clearly identify a device is a "very important criterion of user preference." Also, as stated above, double primary packaging is preferred for some sterile devices.

PACKAGING MATERIALS

Fulfilling the design control procedures discussed above should include using the most appropriate packaging materials available for the device. Although requirements for components, device master records, environmental control, etc., that affect the selection and use of packaging appear throughout the Quality System (QS) regulation, the specific requirements for packaging are in section 820.130. Also the design requirements for Class II, Class III, and the few Class I devices that require design control extend to the broad requirements in 820.30. Device packaging and shipping containers should be designed and constructed to protect the device from adulteration or damage during the customary conditions of processing, storage, handling, and distribution. Closely related label integrity requirements are in section 820.120. Also, the quality of packaging should be considered in relation to the 21 CFR Part 812, Investigational Device Exemptions (IDE's) for clinical evaluations; Part 814, Premarket Approval (PMA) applications; Part 807, Premarket Notification [510(k)] submissions and, of course, customer requirements. Failure to meet these packaging requirements renders a device adulterated and has resulted in recalls of sterile devices.

The package and device should be designed together so that all factors in the product and package system can be considered, such as device sharp edges and severe vacuum stresses. Some other factors to consider are:
End use | Sterilization process  
---|---  
Temperature | Adhesives  
Moisture resistance | Package porosity  
Thermal capacity | Cling resistance  
Device composition | Pressure  
Device size and shape | Vacuum  

It is important that sterile devices and their packaging material meet the requirements of the sterilization process, package sealing method, and intended use. For example, radiation sterilization may discolor packaging and sealing materials, or reduce their functional capabilities. All plastics are somewhat affected by radiation sterilization, occasionally positively, frequently negatively. Consideration should be given to the effect produced and the radiation dose needed to produce an effect. Complete storage and stability data should be compiled for sterile device packaging subjected to radiation or should be obtained from the supplier.

Ethylene oxide (EO) sterilization requires packaging material of sufficient porosity to allow air to leave the package and the gas to rapidly permeate the package, sterilize the product, and then leave the package. Adverse levels of EO residues left on the device harm the patient. Air washing at the end of the cycle reduces residues. Evacuation of the sterilization chamber for air removal, gas fill, and air washing can induce package stress, particularly when the cycle calls for high temperature, pressure, and rapid pressure changes before and after the gas exposure (dwell) period.

**PACKAGE VALIDATION**

Package validation involves two separate validations: 1) the design validation of the package as a component of the device and 2) the process validation of the packaging process. Design validation uses evidence to establish what design specifications will conform with the user needs and the intended use(s) [830.3(z)(2)]. Process validation establishes by objective evidence that a process consistently produces a result or product that meets predetermined specifications [820.3(z)(1)].

The regulation, of course, refers to establishing evidence that the manufacturing steps involved in packaging the device will consistently produce packaging which meets specifications. For example, the process capability of packaging and sealing equipment should be determined during process validation and documented. Validation of the package design shall be performed under actual or simulated use conditions that show the package conforms to its stated intended uses. Risk analysis shall also be included where appropriate.

Design validation results shall include: the design identification, name of the individual(s) performing the validation, method(s) used, and the date. All of this information should be recorded in the design history file. If any significant change is made in the packaging or packaging operation after validation, the new process will need to be revalidated.

One of the most difficult aspects of package validation is determining how many samples to test. The goal is not to over test because of cost considerations while still running sufficient tests to provide statistically valid sampling. Statistical methods of analysis are important in process validation. The following decision tree from *Medical Device and Diagnostic Industry*, "Streamlining Package-Seal Validation," October 1992, provides various methods of statistical analysis. The manufacturer is challenged with determining which statistical method is most applicable to
their individual needs. See Chart 1 below for possible methods of analyzing data. The resulting validation plan should identify, measure, and evaluate the key processes and variables that will require assessment to complete a validation or revalidation of the packaging and the packaging process.

---

**Chart 1** shows various possible methods for analyzing data. Source: *Medical Device and Diagnostic Industry* periodical, October 1992.

**PROCUREMENT, ACCEPTANCE, AND STORAGE**

The packaging associated labeling, sealing methods, acceptance tests, etc., are part of the design output. These design output documents are part of the device master record. The device master record (820.181) should contain appropriate specifications so that the desired packaging components may be purchased, properly stored, and properly used. Suppliers are selected according to 820.50, Purchasing Controls. Manufacturers shall have adequate procedures for approval or rejection of all incoming packaging components such as adhesives, wrapping materials, corner protectors, pouches, cartons, etc. (820.80, discussed in Chapter 10). The supplier may test these components and provide the manufacturer with a protocol for testing and the test results for each batch (i.e., certificate of conformance to purchase specifications). The manufacturer could accept this specific data as sufficient certification based on his assessment of the supplier along with the review of the certificate or order his own testing.
Incoming components should be examined for damage and identity before being used. At a minimum, this examination should include visual inspection. Thereafter, the packaging should be handled and stored in such a way that it is kept clean and safe from damage. Packaging and devices to be sterilized should, obviously, be kept clean before sterilization. For transfusion and infusion assemblies, devices that come in contact with circulating blood or cerebrospinal fluid, intraocular lenses and the surgical instruments used in their implantation, and any device labeled as "pyrogen free" or "nonpyrogenic," the manufacturer should carefully and appropriately control the environment to which the associated packaging materials are exposed in order to minimize bioburden and cellular debris from dead bacteria. Pyrogens primarily arise from cellular debris of gram-negative bacteria.

PACKAGING PROCESS

The packaging operation is a manufacturing process as described in Section 820.70, Production and Process Controls. Other GMP sections also apply to packaging including, but not limited to:

- Receiving, In-Process and Finished Device Acceptance, section 820.80; and
- Distribution, section 820.160.

These sections require adequate controls for components, processing, and test/inspection. The controls necessary for all devices should assure that:

- labeling, whether a separate label or printed on the package, properly reflects the package contents and other labeling requirements;
- the packaging materials meet the device master record specifications;
- only devices approved for release are packaged and released; and
- the packaging operations are performed according to established procedures.

The controls required will vary with the type of device packaged. For example, when a sterile device is packaged, a manufacturer's considerations should include:

- environmental and personnel hygiene control;
- validated operating procedures for sealing equipment;
- inspection to assure package integrity and sanitation; and,
- stringent control of packaged devices marked "sterile" but not yet sterilized.

For a product to be sterilized in-house, either a physical quarantine area or label control should be used to prevent shipment of devices marked sterile, but not yet sterilized. The required level of control is very high. The stringent control also extends to give-away samples not intended for actual use on patients -- samples should be sterile if so labeled because they might be used. One approach is to sell samples at zero cost so that the samples are subjected to all of the company finished product controls.

A written procedure is required by 801.150(e) for **interstate** contract sterilization. The purpose of this requirement is to help prevent the erroneous release of packaged and labeled "sterile" devices that are not yet sterilized even though they appear to be sterile and ready for release. Regardless of whether 801.150(e) applies, the QS regulation
requires sufficient controls as necessary to prevent mixups in complex situations such as contract sterilization. For consistency, a contract is commonly used by manufacturers for interstate and intrastate shipments. Such a contract, and compliance with it, satisfies the applicable GMP requirements.

Section 820.181(d) requires that the device master record include packaging methods and processes. Written instructions should be provided to assure that the necessary controls are understood and consistently implemented. The need for, and the extent of, written instructions should be determined based on the complexity of the operation and the nature of the product. Some products such as radioimmunoassay test kits can deteriorate during packaging if the process is not timed properly. In such cases, written instructions should describe how the device(s) should be handled and expedited during packaging in order to prevent delays, and thus deterioration.

The procedure for testing and/or inspection of finished packages shall be written [(820.80(d)]. To the extent feasible, the testing of finished packages should be quantitative. The packaging of sterile devices should be tested and/or inspected before and after sterilization. This testing is done on a sampling basis. Sampling plans are valid only when a process is in a state-of-control; therefore, the device must be manufactured and packaged using a quality system as described in this manual.

EXHIBITS

The examples that follow will aid a company in preparing product packaging specifications and/or in purchasing standard packaging.

Product Specification: Pouch

This form is used to purchase specific pouches from a standard family of pouches. The finished device manufacturer completes the form with the desired size, material, style, etc. The form refers to other documents which define the technical characteristics of the pouches.

Header Bag (Specification Form)

This specification for a header bag is set up as a checklist with the specifications on the right-hand side and a drawing of the bag on the left. The finished device manufacturer completes the form with the desired technical characteristics, assigns it a part number, and approves the finished document. An interesting idea reflected in this form is the important information block at the bottom of the form. This is a good way to remind personnel of pertinent information that is not strictly a part of the specification yet is vital to the control of this particular item.
SIZE: 5-1/4" x 9-1/4" O.D. 4-1/2" x 8-3/8" I.D.

MATERIAL: #1400 Tyvek® & #1440 Polyethylene/Mylar

STYLE: Plasti-Feel® pouch, 3/8" solid bar seals

APPLICATION:

PRINTING: Plain

Q.A. CLASS: Peelable Products Medical Sterile Class #6, Forms #3274 & #3280

PACKAGING: Packed 1700 per #1073 poly lined carton

MISCELLANEOUS: GPS 001 is applicable unless otherwise specified.
HEADER BAG

CONSTRUCTION

Type: Film, Paper, Other:

Film Gauge:

A. Bag Width:
B. Sealed Length:
C. Header Width:
D. E. F. Seal Width:
G. Header Lip:
H. Poly Lip:
I. Bag Lip:
J. Wicket Position:
K. See seal length:
L. Gap between slit and wicket hole:
M. Distance between wicker holes:
N. Minimum distance between edge of bag and slit:
O. Wicket hole diameter:

Standard 1/2" must be clean cut

Printed: Yes No

PMS color:

Print Position:

Artwork Revision Date:

Additional Information:

TRACEABILITY

Medical industries, Inc. will maintain traceability [GMP] records of each lot back to the raw materials used for the period of three years from date of manufacture.

IMPORTANT INFORMATION

Each packing slip and shipment will carry the following:

1. Customer Part Number
2. Purchase Order Number (customer)
3. Purchase Order Number (vendor)
4. Product Description
5. Order Status (complete or incomplete)
6. Vendor's Name
7. Cert. of Compliance

Each shipping container [carton] shall be labeled with the following information:

1. Carton number
2. Lot number (remains same for date)
3. Purchase order number
4. Size of unit (package)
5. Number of units contained (quantity)
6. Vendor's name
7. Product description
8. Product identification number
14. Storage, Distribution and Installation

INTRODUCTION

Holding and Distribution Procedures
Warehouse Storage
Distribution Records

DEVICE INSTALLATION

EXHIBITS

Finished Product Release Form
Release To Finished Goods/Shipping
Product Shipping Hold
Release From Product Shipping Hold
Partial List of Traceable Devices

INTRODUCTION

The device Quality System (QS) regulation covers the manufacture, storage (820.150), distribution (820.160) and installation (820.170) of finished devices. For manufacturers and importers, distribution is one of the most important steps in their quality system. After a product is distributed, a manufacturer rarely has direct control over the product or how it is used. Thus, it is important that controls be in place to assure that only correctly labeled, packaged and approved finished devices are distributed and, if necessary, installed.

Holding and Distribution Procedures

Section 820.160 requires that the purchase order be reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Manufacturers should have a program to reduce problems in this area. Marketing personnel should be adequately trained. Sales specification flyers and catalogs should be carefully written and kept current to reduce ordering problems. Incoming purchase orders should be checked and ambiguities and errors resolved. After receipt by appropriately trained personnel, orders should be reviewed immediately. If purchase orders are reviewed late in the manufacturing process or just before distribution, the value of the review may be significantly reduced. Where the customer includes specifications, each specified parameter should be checked against the corresponding parameter for the device. A checklist of device parameters may be a helpful tool for this review and should be filed with, or keyed to, the purchase order.

The QS regulation (820.60), Identification, requires manufacturers to set up and maintain identity control of their products from component receipt, production, distribution and through installation to prevent mixups. The regulation also requires that written procedures be provided for control and distribution of finished devices (820.160).
purpose of this requirement is to assure that only approved devices are distributed. Each manufacturer should determine what written procedures are needed to assure that only "approved for release" devices are distributed from the manufacturer. If a manufacturer believes written procedures will not contribute to assuring that only approved for release devices are distributed by their manufacturer, they should be able to defend their decision. For example, the control is integrated into the activities required to package the device or to complete the device history record. This flexibility is allowed by section 820.5, Quality system, of the QS regulation.

Many manufacturers mark their released finished devices or identify them by location or packaging so that a simple visual check is sufficient to indicate whether the product is acceptable to release for distribution. For example, radiation-emitting electronic products are subject to a performance standard. The application of the certification label is often the last step in approving product release for distribution, and this label is used to distinguish such devices. After final release, the crating of large equipment is a very distinguishing feature. These types of operations may preclude the need for a separate written procedure.

For interstate contract sterilization, 21 C.F.R. section 801.150(e) requires a written agreement between the parties which details the necessary procedures to help prevent the erroneous release of packaged and labeled "sterile" but not yet sterilized devices that appear to be, but are not, ready for release. Regardless of whether 801.150(e) applies, the QS regulation requires controls, as necessary, to prevent mixups in complex situations such as contract sterilization. For consistency, a contract as described by 801.150(e) is commonly used by manufacturers for interstate and intrastate shipments. Compliance with such a contract satisfies the applicable GMP requirements. (See Chapter 10, Purchasing and Acceptance Activities, and Compliance Policy Guide 7382.830B for details.)

Sometimes manufacturers need to ship "finished devices" that have not been officially released because the final test data is not yet available. The critical factor is that the device still remains under the manufacturer's control. The most common example occurs when a manufacturer is waiting for the results from biological indicator tests. FDA permits manufacturers to ship such devices under quarantine to their own controlled warehouses where the devices may be readily recalled prior to any use, if the need arises. Manufacturers should not ship non-released devices to routine distributors or anyone outside of their direct control. Non-released products or products on "hold" for any quality reason should be controlled to prevent release. A suitable control is quarantine with a label on the units, pallets, etc., to indicate their status.

**Warehouse Storage**

Storage should always be done under systematic, orderly conditions (820.150). Manufacturers should use a first-in, first-out (FIFO) distribution system when fitness for use of a device deteriorates over time (820.150).

When a controlled environment is necessary to prevent abnormal deterioration, the environment should be specified, controlled, and monitored according to sections 820.70 (c) (see Chapter 6, Buildings and Environment). Environmental specifications, such as storage temperature, should be included in the device master record.

The storage and handling of devices to be distributed may involve extensive activities (820.140 and 820.150). For example, damaged, recalled or returned devices should be suitably marked and segregated from devices acceptable for release (820.86). Returned devices should be handled and stored such that the cause of failure or other useful information is not destroyed. Returned defective devices should be formally investigated according to 820.100 Corrective and Preventive Action and any associated complaints investigated according to 820.198. Therefore, manufacturers will need controls to assure that returned defective devices do not dead-end in the warehouse, but are expeditiously routed to the appropriate department for evaluation, investigation, conclusions and follow-up (see Chapter 15, Complaint Files).

**Distribution Records**

Quality System section 820.184, Device History Record (DHR), requires manufacturers of devices to maintain basic records for:

- dates of manufacture,
- the quantity manufactured,
- quantity released for distribution,
Section 820.160, Distribution, requires the following records:

- name and address of the initial consignee,
- identification and quantity of devices shipped,
- date shipped, and
- any control number used.

Some of the above information necessary for the distribution records is a duplicate of Device History Record (DHR) requirements. These duplications may be copied or transferred electronically from the DHR. If appropriate, a manufacturer may combine the records by adding the distribution information to the DHR.

In addition to the above requirements, manufacturers of implantable devices and life sustaining devices, the failure of which during use could result in significant injury to the user, are required to establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and, where appropriate, components (820.65). A partial list of traceable devices that meet this definition is printed at the end of this chapter.

Distribution records may be the same as, or part of, the normal business records. Generation of a separate record is not required unless the business records are not readily available, e.g., not maintained at the same establishment as the device history record and not readily retrievable electronically. Many manufacturers, also keep distribution records for billing and market survey purposes.

Manufacturers of radiological electronic products listed in 21 CFR 1002.1, Record and Reporting Requirements By Product, shall maintain distribution records that will enable them to trace specific products or production lots to distributors, or to dealers in those instances in which the manufacturer distributes directly to dealers (See 21 CFR 1002.30, Records to be Maintained by Manufacturers).

Distribution records shall be kept for a period of time equivalent to the design life and expected life of the device, but in no case less than two years from the date of release for commercial distribution by the manufacturer [820.180(b)]. The intent of this requirement is support for potential repairs, corrective actions and recalls. Each manufacturer should make a prudent decision whether to discard records or keep all, or part, of them for a longer period. When requested, distribution records shall be made available to FDA investigators for review and copying during normal business hours.

**DEVICE INSTALLATION**

Section 820.170 on installation requires that each manufacturer establish and maintain adequate installation and inspection instructions and, where appropriate, testing procedures. The purpose of this requirement is to ensure that the device is properly installed and will perform as intended after installation. This regulation applies to medical device systems and complex devices that require set up and adjustment at the location where they are to be used. For example, before a diagnostic x-ray machine can be used, it has to be installed and adjusted and the performance checked. Cardiopulmonary bypass machines also require set up and adjustment at the user location. Manufacturers of such devices shall:

- install the device, or have it installed by a representative;
- inspect and test, as appropriate, the device after installation to assure the device will perform as intended; or
- provide adequate instructions and procedures for proper installation by another party.
These instructions and procedures for proper installation by the manufacturer's representative, user, or third party (820.170) shall include instructions on how to determine that the installed device is safe, performing satisfactorily and ready for use. Safety checks at installation refer to safety aspects directly related to the installation and setup activities and not to intrinsic safety features that have already been checked during final acceptance testing at the factory.

The instructions and procedures shall be distributed with the device or otherwise made available to the person installing the device. Such procedures and instructions are part of the device master record and generally include a checklist for the installer to make certain that all necessary installation and checkout activities have been performed correctly. The installer should complete the checklist. If available to the manufacturer, the filled-in checklist or other installation records are part of the device history record.

Installation and servicing are related activities. Therefore, see Chapter 16, Servicing, for more information.

EXHIBITS

Various forms to show that devices are finished and may be released or stopped from release and a list of some traceable devices are briefly described below and then exhibited.

**Finished Product Release Form**

This exhibit shows an example of a finished product release form which is actually a checklist for the manufacturing and QC departments of an in vitro diagnostic manufacturer to show that all required processes have been completed. The checklist acts as a reminder of the acceptance forms that are needed for a product and has space for the manufacturing and QC people to indicate that these forms have been completed and reviewed. Finally there is space for the designees to approve or disapprove the lot for release and for comments, if needed.

**Release To Finished Goods/Shipping**

This exhibit is a release form as described above except that it is for various hardware products. The employee writes in the specification for the product being released.

**Product Shipping Hold**

This exhibit is an example of a form used to stop the shipping of a finished device for reasons related to safety, performance, reliability, regulatory compliance, or other quality requirements.

**Release From Product Shipping Hold**

This is a form used to release a finished device from a stop shipment order. Because stop orders are always significant, this release form requires a signature by key management.

**Partial List of Traceable Devices**

This exhibit lists many of the devices for which a manufacturer must adopt a method of device tracking and the citation to 21 C.F.R. for the device.

It is required that implantable devices and life sustaining devices, whose failure during use as described on the label, could result in significant injury to the user, establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices. Where appropriate, this traceability rule also applies to
components. These procedures should facilitate corrective action. This identification should be documented in the device history record. Many of these devices were formerly called critical devices.

<table>
<thead>
<tr>
<th>FINISHED PRODUCT RELEASE</th>
<th>Form No.</th>
<th>Rev.</th>
<th>Sheet 1 of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form Approved by:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECN notes:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Title: AMYLASE SET**

<table>
<thead>
<tr>
<th>Packaging lot number</th>
<th>CATALOG Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AM-389-01</td>
</tr>
<tr>
<td></td>
<td>AM-389-02</td>
</tr>
</tbody>
</table>

The device history documents below were reviewed by 6 Circle one form number in 2, 5 & 7 below.

<table>
<thead>
<tr>
<th>MFG</th>
<th>QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Form # 9926</td>
<td>Product flow sheet</td>
</tr>
<tr>
<td>2. Form # 1077 or 1078</td>
<td>Iodine solution</td>
</tr>
<tr>
<td>3. Form # 1082</td>
<td>Substrate solution</td>
</tr>
<tr>
<td>4. Form # 1083</td>
<td>Substrate tube filling sheet</td>
</tr>
<tr>
<td>5. Form # 1084 or 1085</td>
<td>Iodine filling sheet</td>
</tr>
<tr>
<td>6. Form # 1086</td>
<td>Packaging record</td>
</tr>
<tr>
<td>7. Form # QC-PP-07 or QC-PP-01</td>
<td>Finished device specification</td>
</tr>
</tbody>
</table>

Comments

Sign. MFG Designee APP. Yes or No

Comments

Signature QC Designee Approved Yes or No

<table>
<thead>
<tr>
<th>RELEASE TO FINISHED GOODS/SHIPPING</th>
<th>Form # Release-110</th>
<th>Rev. B</th>
<th>Sheet 1 of 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form Approved by:</td>
<td></td>
<td>Date 4-15-1974</td>
<td></td>
</tr>
<tr>
<td>ECN notes:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Type of Product: [ ] Cable [ ] Instrument [ ] Spare/Replacement part/assembly

<table>
<thead>
<tr>
<th>PRODUCT NAME</th>
<th>Part Number</th>
<th>Serial / Lot Number</th>
</tr>
</thead>
</table>

### QSR Manual

<table>
<thead>
<tr>
<th>Inspection Specification Number</th>
<th>Revision</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRODUCT STATUS</strong></td>
<td>Circle yes or no 9</td>
</tr>
<tr>
<td>1. Final inspection complete per standards set forth in the QC manual and device inspection specification?</td>
<td>YES</td>
</tr>
<tr>
<td>2. Device history record packet present?</td>
<td>YES</td>
</tr>
</tbody>
</table>

**If the answer to 1 or 2 is NO, return lot to Production.**

| 3. Has Final Inspection performed a simulated use test? | YES | NO |
| 4. An identified final test data sheet is with the unit? | YES | NO |

**Comments**

Signature QC Designee Approved | YES | NO |
Quantity Released | Date |

---

### PRODUCT SHIPPING HOLD

**BY QUALITY ASSURANCE DEPARTMENT**

The product listed below is on **SHIPPING HOLD** and under NO circumstances is to be shipped from the factory or any field office without the written approval of the Director, Quality Assurance.

**PRODUCT:**

HOLD STARTING DATE:

**CLASSIFICATION OF HOLD**

- [ ] EFFICACY
- [ ] RELIABILITY
- [ ] STERILITY
- [ ] OTHER (describe)

[ ] SAFETY
[ ] REGULATORY COMPLIANCE
[ ] GOOF UP

**REASON FOR HOLD:**

**ACTION REQUIRED BEFORE RELEASE:**

**MDR/RECALL NOTES:**

Sign., DIRECTOR, QUALITY ASSURANCE
### Partial List of Traceable Devices
<table>
<thead>
<tr>
<th>CFR Cite</th>
<th>Classification Name of Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>868.1200</td>
<td>Indwelling blood oxygen partial pressure (P$_{O2}$) analyzer</td>
</tr>
<tr>
<td>868.2375</td>
<td>Breathing frequency monitor</td>
</tr>
<tr>
<td>868.5090</td>
<td>Emergency airway needle</td>
</tr>
<tr>
<td>868.5160(a)</td>
<td>Gas machine for anesthesia</td>
</tr>
<tr>
<td>868.5240</td>
<td>Anesthesia breathing circuit</td>
</tr>
<tr>
<td>868.5400</td>
<td>Electroanesthesia apparatus</td>
</tr>
<tr>
<td>868.5440</td>
<td>Portable oxygen generator</td>
</tr>
<tr>
<td>868.5470</td>
<td>Hyperbaric chamber (Monoplace)</td>
</tr>
<tr>
<td>868.5610</td>
<td>Membrane lung for long term pulmonary support</td>
</tr>
<tr>
<td>868.5650</td>
<td>Esophageal obturator</td>
</tr>
<tr>
<td>868.5720</td>
<td>Bronchial tube</td>
</tr>
<tr>
<td>868.5730</td>
<td>Tracheal tube</td>
</tr>
<tr>
<td>868.5740</td>
<td>Tracheal/bronchial differential ventilation tube</td>
</tr>
<tr>
<td>868.5750</td>
<td>Inflatable tracheal tube cuff</td>
</tr>
<tr>
<td>868.5800</td>
<td>Tracheostomy tube and tube off</td>
</tr>
<tr>
<td>868.5810</td>
<td>Airway connector</td>
</tr>
<tr>
<td>868.5830</td>
<td>Autotransfusion apparatus</td>
</tr>
<tr>
<td>868.5895</td>
<td>Continuous ventilator</td>
</tr>
<tr>
<td>868.5905</td>
<td>Noncontinuous ventilator (IPPB)</td>
</tr>
<tr>
<td>868.5915</td>
<td>Manual emergency ventilator</td>
</tr>
<tr>
<td>868.5925</td>
<td>Powered emergency ventilator</td>
</tr>
<tr>
<td>868.5935</td>
<td>External negative pressure ventilator</td>
</tr>
</tbody>
</table>

**PART 870 -- CARDIOVASCULAR DEVICES**

<table>
<thead>
<tr>
<th>CFR Cite</th>
<th>Classification Name of Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>870.1025</td>
<td>Arrhythmia detector and alarm</td>
</tr>
<tr>
<td>870.1330</td>
<td>Catheter guide wire</td>
</tr>
<tr>
<td>870.1360</td>
<td>Trace microsphere</td>
</tr>
<tr>
<td>870.1750</td>
<td>External programmable pacemaker pulse generator</td>
</tr>
<tr>
<td>870.1800</td>
<td>Withdrawal-infusion pump</td>
</tr>
<tr>
<td>870.3250</td>
<td>Vascular clip</td>
</tr>
<tr>
<td>870.3260</td>
<td>Vena cava clip</td>
</tr>
<tr>
<td>CPT Code</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>870.3300</td>
<td>Arterial embolization device</td>
</tr>
<tr>
<td>870.3375</td>
<td>Cardiovascular intravascular filter</td>
</tr>
<tr>
<td>870.3450</td>
<td>Vascular graft prosthesis of less than 6 millimeters diameter</td>
</tr>
<tr>
<td>870.3460</td>
<td>Vascular graft prosthesis of 6 millimeters and greater diameter</td>
</tr>
<tr>
<td>870.3470</td>
<td>Intracardiac patch or pledget made of polypropylene, polyethylene terephthalate, or polytetrafluoroethylene</td>
</tr>
<tr>
<td>870.3535</td>
<td>Intra-aortic balloon and control system</td>
</tr>
<tr>
<td>870.3545</td>
<td>Ventricular bypass (assist) device</td>
</tr>
<tr>
<td>870.3600</td>
<td>External pacemaker pulse generator</td>
</tr>
<tr>
<td>870.3610</td>
<td>Implantable pacemaker pulse generator</td>
</tr>
<tr>
<td>870.3620</td>
<td>Pacemaker lead adaptor</td>
</tr>
<tr>
<td>870.3650</td>
<td>Pacemaker polymeric mesh bag</td>
</tr>
<tr>
<td>870.3670</td>
<td>Pacemaker charger</td>
</tr>
<tr>
<td>870.3680</td>
<td>Cardiovascular permanent or temporary pacemaker electrode</td>
</tr>
<tr>
<td>870.3690</td>
<td>Pacemaker programmers</td>
</tr>
<tr>
<td>870.3710</td>
<td>Pacemaker repair or replacement material</td>
</tr>
<tr>
<td>870.3800</td>
<td>Annuloplasty ring</td>
</tr>
<tr>
<td>870.3850</td>
<td>Carotid sinus nerve stimulator</td>
</tr>
<tr>
<td>870.3925</td>
<td>Replacement heart valve</td>
</tr>
<tr>
<td>870.4320</td>
<td>Cardiopulmonary bypass pulsatile flow generator</td>
</tr>
<tr>
<td>870.4350</td>
<td>Cardiopulmonary bypass oxygenator</td>
</tr>
<tr>
<td>870.4360</td>
<td>Nonroller-type cardiopulmonary bypass blood pump</td>
</tr>
<tr>
<td>870.4370</td>
<td>Roller-type cardiopulmonary bypass blood pump</td>
</tr>
<tr>
<td>870.5200</td>
<td>External cardiac compressor</td>
</tr>
<tr>
<td>870.5225</td>
<td>External counter-pulsating device</td>
</tr>
<tr>
<td>870.5300</td>
<td>DC-defibrillator (including paddles)</td>
</tr>
<tr>
<td>870.5550</td>
<td>External transcutaneous cardiac pacemaker (noninvasive)</td>
</tr>
<tr>
<td>---</td>
<td>Percutaneous transluminal coronary angioplasty (PTCA) balloon dilation catheter</td>
</tr>
<tr>
<td>---</td>
<td>Automatic implanted cardioverter defibrillator system</td>
</tr>
<tr>
<td><strong>PART 872 -- DENTAL DEVICES</strong></td>
<td></td>
</tr>
<tr>
<td>872.3640</td>
<td>Endosseous implant</td>
</tr>
<tr>
<td><strong>PART 874 -- EAR, NOSE, AND THROAT DEVICES</strong></td>
<td></td>
</tr>
<tr>
<td>872.3620</td>
<td>Ear, nose and throat synthetic polymer material</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>874.3695</td>
<td>Mandibular implant facial prosthesis</td>
</tr>
<tr>
<td>874.3730</td>
<td>Laryngeal prosthesis (Taub design)</td>
</tr>
<tr>
<td>874.3820</td>
<td>Endolymphaic shunt</td>
</tr>
<tr>
<td>874.3850</td>
<td>Endolymphaic shunt tube with valve</td>
</tr>
<tr>
<td>874.3930</td>
<td>Tympanotomy tube with semipermeable membrane</td>
</tr>
<tr>
<td>---</td>
<td>ear, nose, throat natural polymer-collagen material</td>
</tr>
<tr>
<td>PART 876</td>
<td>GASTROENTEROLOGY-UROLOGY DEVICES</td>
</tr>
<tr>
<td>876.3350</td>
<td>Penile inflatable implant</td>
</tr>
<tr>
<td>876.5270</td>
<td>Implanted electrical urinary continence device</td>
</tr>
<tr>
<td>876.5540</td>
<td>A-V shunt cannula</td>
</tr>
<tr>
<td>876.5630</td>
<td>Peritoneal dialysis system and accessories</td>
</tr>
<tr>
<td>876.5820</td>
<td>Hemodialysis system and accessories, dialysate concentrate, hollow fiber capillary dialyzers, disposable dialyzers, high permeability dialyzers, parallel flow dialyzers, single coil dialyzers, twin coil dialyzers, single needle dialysis set, dialysate delivery systems</td>
</tr>
<tr>
<td>876.5870</td>
<td>Sorbent hemoperfusion system</td>
</tr>
<tr>
<td>876.5880</td>
<td>Isolated kidney perfusion and transport system and accessories</td>
</tr>
<tr>
<td>876.5955</td>
<td>Peritoneo-venous shunt</td>
</tr>
<tr>
<td>46 FR 7566</td>
<td>Urethral sphincter prosthesis</td>
</tr>
<tr>
<td>46 FR 7566</td>
<td>Urethral replacement</td>
</tr>
<tr>
<td>PART 878</td>
<td>GENERAL AND PLASTIC SURGERY DEVICES</td>
</tr>
<tr>
<td>42 FR 63474</td>
<td>Absorbable surgical sutures</td>
</tr>
<tr>
<td>42 FR 63474</td>
<td>Nonabsorbable surgical sutures</td>
</tr>
<tr>
<td>879.4520</td>
<td>Polytetrafluoroethylene (Teflon) injectable</td>
</tr>
<tr>
<td>878.3300</td>
<td>Surgical mesh</td>
</tr>
<tr>
<td>878.3500</td>
<td>Polytetrafluoroethylene with carbon fibers composite implant material</td>
</tr>
<tr>
<td>878.3530</td>
<td>Inflatable breast prosthesis</td>
</tr>
<tr>
<td>878.3540</td>
<td>Silicone gel-filled breast prosthesis</td>
</tr>
<tr>
<td>---</td>
<td>Implanted mammary prosthesis of composite saline and gel-filled design</td>
</tr>
<tr>
<td>878.3610</td>
<td>Esophageal prosthesis</td>
</tr>
<tr>
<td>878.3720</td>
<td>Tracheal prosthesis</td>
</tr>
<tr>
<td>Code</td>
<td>Item Description</td>
</tr>
<tr>
<td>----------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>878.4300</td>
<td>Implantable clip</td>
</tr>
<tr>
<td>878.4750</td>
<td>Implantable staple</td>
</tr>
<tr>
<td>---</td>
<td>Maxillofacial prosthesis</td>
</tr>
</tbody>
</table>

**PART 880 -- GENERAL HOSPITAL AND PERSONAL USE DEVICES**

<table>
<thead>
<tr>
<th>Code</th>
<th>Item Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>880.5130</td>
<td>Infant radiant warmer</td>
</tr>
<tr>
<td>880.5400</td>
<td>Neonatal incubator</td>
</tr>
<tr>
<td>880.5410</td>
<td>Neonatal transport incubator</td>
</tr>
<tr>
<td>880.5725</td>
<td>Infusion pump</td>
</tr>
<tr>
<td>---</td>
<td>Implanted infusion pump</td>
</tr>
</tbody>
</table>

**PART 882 -- NEUROLOGICAL DEVICES**

<table>
<thead>
<tr>
<th>Code</th>
<th>Item Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>882.5030</td>
<td>Methyl methacrylate for aneurysmorrhaphy</td>
</tr>
<tr>
<td>882.5150</td>
<td>Intravascular occluding catheter</td>
</tr>
<tr>
<td>882.5200</td>
<td>Aneurysm clip</td>
</tr>
<tr>
<td>882.5225</td>
<td>Implanted malleable clip</td>
</tr>
<tr>
<td>882.5250</td>
<td>Burr hole cover</td>
</tr>
<tr>
<td>882.5300</td>
<td>Methyl methacrylate for cranioplasty</td>
</tr>
<tr>
<td>882.5320</td>
<td>Preformed alterable cranioplasty plate</td>
</tr>
<tr>
<td>882.5330</td>
<td>Preformed nonalterable cranioplasty plate</td>
</tr>
<tr>
<td>882.5360</td>
<td>Cranioplasty plate fastener</td>
</tr>
<tr>
<td>882.5550</td>
<td>Central nervous system fluid shunt and components</td>
</tr>
<tr>
<td>882.5820</td>
<td>Implanted cerebellar stimulator</td>
</tr>
<tr>
<td>882.5830</td>
<td>Implanted diaphragmatic/phrenic nerve stimulator</td>
</tr>
<tr>
<td>882.5840</td>
<td>Implanted intracerebral/subcortical stimulator for pain relief</td>
</tr>
<tr>
<td>882.5850</td>
<td>Implanted spinal cord stimulator for bladder evacuation</td>
</tr>
<tr>
<td>882.5860</td>
<td>Implanted neuromuscular stimulator</td>
</tr>
<tr>
<td>882.5870</td>
<td>Implanted peripheral nerve stimulator for pain relief</td>
</tr>
<tr>
<td>882.5880</td>
<td>Implanted spinal cord stimulator for pain relief</td>
</tr>
<tr>
<td>882.5880</td>
<td>Epidural spinal electrode</td>
</tr>
<tr>
<td>882.5900</td>
<td>Preformed craniosynostosis strip</td>
</tr>
<tr>
<td>882.5910</td>
<td>Dura substitute</td>
</tr>
<tr>
<td>882.5950</td>
<td>Artificial embolization device</td>
</tr>
<tr>
<td>---</td>
<td>Lyophilized human (cadaver) dura mater</td>
</tr>
<tr>
<td>---</td>
<td>Stabilized epidural spinal electrode</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>QSR Manual</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>Implanted intracranial pressure monitor</td>
</tr>
<tr>
<td>---</td>
<td>Totally implanted spinal cord stimulator for pain relief</td>
</tr>
</tbody>
</table>

**PART 884 -- OBSTETRICAL AND GYNECOLOGICAL DEVICES**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>884.5360</td>
<td>Contraceptive intrauterine device (IUD) and introducer</td>
</tr>
<tr>
<td>884.5380</td>
<td>Contraceptive tubal occlusion device (TOD) and introducer</td>
</tr>
</tbody>
</table>

**PART 886 -- OPHTHALMIC DEVICES**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>886.3300</td>
<td>Absorbable implant (scleral buckling method)</td>
</tr>
<tr>
<td>886.3400</td>
<td>Keratoprosthesis</td>
</tr>
<tr>
<td>886.3600</td>
<td>Intraocular lens</td>
</tr>
<tr>
<td>886.3920</td>
<td>Eye valve implant</td>
</tr>
</tbody>
</table>

**PART 888 -- ORTHOPEDIC DEVICES**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>888.3000</td>
<td>Bone Cap</td>
</tr>
<tr>
<td>888.3010</td>
<td>Bone fixation cerclage</td>
</tr>
<tr>
<td>888.3020</td>
<td>Intramedullary fixation rod</td>
</tr>
<tr>
<td>888.3025</td>
<td>Passive tendon prosthesis</td>
</tr>
<tr>
<td>888.3027</td>
<td>Polymethylmethacrylate (PMMA) bone cement</td>
</tr>
<tr>
<td>888.3030</td>
<td>Single/multiple component metallic bone fixation appliance and accessories</td>
</tr>
<tr>
<td>888.3040</td>
<td>Smooth or threaded metallic bone fixation fastener</td>
</tr>
<tr>
<td>888.3050</td>
<td>Spinal interlaminal fixation orthosis</td>
</tr>
<tr>
<td>888.3060</td>
<td>Spinal intervertebral body fixation orthosis</td>
</tr>
<tr>
<td>888.3100</td>
<td>Ankle joint metal/composite semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3110</td>
<td>Ankle joint metal/polymer semiconstrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3120</td>
<td>Ankle joint metal/polymer non-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3150</td>
<td>Elbow joint metal/metal or metal/polymer constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3160</td>
<td>Elbow joint metal/polymer semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3170</td>
<td>Elbow joint radial (hemi-elbow) polymer prosthesis</td>
</tr>
<tr>
<td>888.3180</td>
<td>Elbow joint humeral (hemi-elbow) metallic uncemented prosthesis</td>
</tr>
<tr>
<td>888.3200</td>
<td>Finger joint metal/metal constrained uncemented prosthesis</td>
</tr>
<tr>
<td>888.3210</td>
<td>Finger joint metal/metal constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3220</td>
<td>Finger joint metal/polymer constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3230</td>
<td>Finger joint polymer constrained prosthesis</td>
</tr>
<tr>
<td>888.3300</td>
<td>Hip joint metal constrained cemented or uncemented prosthesis</td>
</tr>
<tr>
<td>888.3310</td>
<td>Hip joint metal/polymer constrained cemented or uncemented prosthesis</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>888.3320</td>
<td>Hip joint metal/metal semi-constrained, with a cemented acetabular component, prosthesis</td>
</tr>
<tr>
<td>888.3330</td>
<td>Hip joint metal/metal semi-constrained, with an uncemented acetabular component, prosthesis</td>
</tr>
<tr>
<td>888.3340</td>
<td>Hip joint metal/composite semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3350</td>
<td>Hip joint metal/polymer semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3360</td>
<td>Hip joint femoral (hemi-hip) metallic cemented or uncemented prosthesis</td>
</tr>
<tr>
<td>888.3370</td>
<td>Hip joint (hemi-hip) acetabular metal cemented prosthesis</td>
</tr>
<tr>
<td>888.3380</td>
<td>Hip joint femoral (hemi-hip) trunnion-bearing metal/polyacetal cemented prosthesis</td>
</tr>
<tr>
<td>888.3390</td>
<td>Hip joint femoral (hemi-hip metal/polymer cemented or uncemented prosthesis</td>
</tr>
<tr>
<td>888.3400</td>
<td>Hip joint femoral (hemi-hip) metallic resurfacing prosthesis</td>
</tr>
<tr>
<td>888.3410</td>
<td>Hip joint metal/polymer semi-constrained resurfacing cemented prosthesis</td>
</tr>
<tr>
<td>888.3480</td>
<td>Knee joint femorotibial metallic constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3490</td>
<td>Knee joint femorotibial metal/composite non-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3500</td>
<td>Knee joint femorotibial metal/composite semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3510</td>
<td>Knee joint femorotibial metal/polymer constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3520</td>
<td>Knee joint femorotibial metal/polymer non-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3530</td>
<td>Knee joint femorotibial metal/polymer semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3540</td>
<td>Knee joint patellofemoral polymer/metallc semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3550</td>
<td>Knee joint patellofemorotibial polymer/metal/metal constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3560</td>
<td>Knee joint patellofemorotibial polymer/polymer semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3570</td>
<td>Knee joint femoral (hemi-knee) metallic uncemented prosthesis</td>
</tr>
<tr>
<td>888.3580</td>
<td>Knee joint patellar (hemi-knee) metallic resurfacing uncemented prosthesis</td>
</tr>
<tr>
<td>888.3590</td>
<td>Knee joint tibial (hemi-knee) metallic resurfacing uncemented prosthesis</td>
</tr>
<tr>
<td>888.3640</td>
<td>Shoulder joint metal/metal or metal/polymer constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3650</td>
<td>Shoulder joint metal/polymer non-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3660</td>
<td>Shoulder joint metal/polymer semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3680</td>
<td>Shoulder joint glenoid (hemi-shoulder) metallic cemented prosthesis</td>
</tr>
<tr>
<td>888.3690</td>
<td>Shoulder joint humeral (hemi-shoulder) metallic uncemented prosthesis</td>
</tr>
<tr>
<td>888.3720</td>
<td>Toe joint polymer constrained prosthesis</td>
</tr>
<tr>
<td>888.3730</td>
<td>Toe joint phalangeal (hemi-toe) polymer prosthesis</td>
</tr>
<tr>
<td>888.3750</td>
<td>Wrist joint carpal lunate polymer prosthesis</td>
</tr>
<tr>
<td>888.3760</td>
<td>Wrist joint carpal scaphoid polymer prosthesis</td>
</tr>
<tr>
<td>888.3770</td>
<td>Wrist joint carpal trapezium polymer prosthesis</td>
</tr>
<tr>
<td>888.3780</td>
<td>Wrist joint polymer constrained prosthesis</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>888.3790</td>
<td>Wrist joint metal constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3800</td>
<td>Wrist joint metal/polymer semi-constrained cemented prosthesis</td>
</tr>
<tr>
<td>888.3810</td>
<td>Wrist joint ulna (hemi-wrist) polymer prosthesis</td>
</tr>
</tbody>
</table>
15. Complaints

INTRODUCTION

Complaint Handling System
Complaint Responsibility
MDR Reportable Complaints
Complaint Records
Investigation Records
File Accessibility and Location
Non-medical Complaints
Complaint Analysis

DEVICE FAILURE ANALYSIS

FEEDBACK FOR QA SYSTEM

COMPLAINT SOURCES

MEDICAL DEVICE REPORTING

Who Must Report
When to Report
Individual Adverse Event Reports
Written MDR Procedures
MDR Event Files
How to Maintain MDR Event Files

ADDITIONAL MDR GUIDANCE

Reports of Removals and Corrections

EXHIBITS

Complaint Processing Procedure and Forms
MedWatch Forms

INTRODUCTION

Section 820.3(b) of the Quality Systems regulation defines a complaint as "any written, electronic, or oral communication that alleges deficiencies related to the
identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.” All medical device manufacturers are subject to the complaint requirements in 21 CFR Part 820, Quality System regulation and to the reporting requirements in 21 CFR Part 803, Medical Device Reporting (MDR) regulation. A complaint is any indication of the failure of a device to meet customer or user expectations for quality or to meet performance specifications. A complaint may be lodged against any finished device that had been released for distribution. Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications is subject to the provisions of 21 CFR 820.198, Complaint Files.

The sources of oral and written complaints are numerous. A manufacturer can receive this information via telephone, facsimile, written correspondence, sales representatives, service representatives, scientific articles, and FDA or internal analyses. Information will also be submitted by health care professionals, lay users, consumers, user facilities and distributors on the MedWatch Forms FDA 3500 and FDA 3500A.

Manufacturers are required to review, evaluate, and, when appropriate, investigate complaints, establish and maintain written procedures describing the process used to perform these activities, and designate a responsible individual or entity to perform these tasks. Complaints concerning death, serious injury or malfunctions, as defined in the MDR regulation, shall be reported to FDA as discussed later. Manufacturers of any class of medical devices are never exempted from the Quality System regulation complaint requirements (820.198) nor the general record requirements (820.180) which permit FDA review and copying of these records. Complaint file requirements are necessary to make certain manufacturers have adequate quality systems for investigating complaints and taking corrective action. Access to complaint files, device-related death and injury reports, and complaints about device defects enables FDA to determine if a manufacturer's quality system and corrective actions are adequate.

Manufacturers can identify problems with device component, labeling and packaging quality by several methods. To meet all GMP requirements these identification methods should include a review and evaluation of all complaints, failed devices, and service or repair requests. Complaints and service or repair requests are important sources of feedback information for a quality system. Finished devices that are returned for service or repair may meet the complaint requirements identified in section 820.198; therefore, these service or repair requests shall be evaluated to determine if they are complaints. Service or repair data shall be reviewed [820.200(b)&(e)] to identify systematic problems and problems that may qualify as complaints. When these problems are identified they should be processed as complaints according to the requirements in 820.198.

Complaint data, in conjunction with product audits, QA systems audits, operational analyses, inspection and test data, etc., is used by the quality assurance organization to:

- identify poor performance in the overall quality system, particularly faulty design of devices, and faulty manufacturing processes;
- aid in implementing solutions to these quality problems;
- verify confidence in, and improve the performance of the quality system;
- improve the safety and performance of devices;
- reduce medical device reporting;
- reduce costs and improve production schedules;
- reduce employee confusion;
● improve customer relations by reducing the frequency of problems, complaints, and recalls; and,

● assure compliance with device regulations and consensus standards.

Complaint Handling System

An effective complaint handling system is an extremely important part of any quality system. Even manufacturers who have not received complaints should be prepared to receive and process them. Manufacturers should understand that any complaint received on a product shall be evaluated and, if necessary, thoroughly investigated and analyzed, and corrective actions shall be taken. The results of this evaluation should lead to a conclusion regarding whether the complaint was valid, what the cause of the complaint was, and what action is necessary to prevent further occurrences. Complaints cannot be ignored. They are an excellent indicator of problems with the use, design, and/or manufacture of a product. A single complaint that is thoroughly investigated may lead a company to take remedial or corrective action. It may also take an ongoing analysis of numerous complaints before a trend is spotted that causes a company to initiate changes in their product, labeling, packaging or distribution.

Using written procedures for handling complaints increases confidence that all complaints will be handled properly. Written procedures should be provided to employees to facilitate communication, maintain consistency, and reduce quality problems. Written procedures for the receiving, reviewing and evaluating of complaints by a formally designated unit shall be established and maintained in accordance with 820.198, Complaint Files, and 820.40, Document Controls, respectively. The procedures should include the need for complaints to be evaluated in accordance with 820.100, Corrective and Preventive Action.

The complaint files shall be maintained in accordance with the general record keeping requirements of 820.180. All complaint files are to be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer. The written procedure should specify: authority; responsibilities; and the process to follow in receiving, reviewing, and investigating complaints. However, for very small manufacturers where division of work is minimal, and authorities and responsibilities are obvious, the GMP requirements as detailed in 820.198 in conjunction with appropriate forms may be sufficient as a protocol for handling complaints.

Although FDA does not specify a standard complaint handling system, the GMP requirements do specify certain actions that shall be included in any system. Manufacturers shall:

● document, review, evaluate, and file all complaints;
● formally designate a unit or individual to perform these activities;
● determine if an investigation is necessary;
● record the reason if no investigation is made;
● assign responsibility for deciding when not to investigate; and,
● determine if the complaint requires an MDR report.

Complaint Responsibility

Manufacturers shall formally assign responsibility for maintaining complaint files and conducting complaint investigations to individuals or an organizational unit. Under 820.25(b) it is the manufacturer's responsibility to ensure that personnel are properly trained to adequately perform their duties. These employees shall have the proper education and training to process complaints. Any difficulty noted in employees performing required tasks for proper complaint handling may be an indication that additional training is needed. Training shall be documented.
The person(s) assigned to review complaints should have a thorough knowledge of the product line in order to make an informed, reasonable decision as to the severity and significance of a complaint and to decide whether an investigation is necessary. If it is decided that an investigation is not necessary, a record shall be made of the rationale used to arrive at this decision. The record must identify the individual responsible for making this decision.

Executive management should ensure that adequate resources are provided, including trained personnel, to the designated complaint handling unit within the company. The activities of the unit should be assessed on a regular basis, and corrections made if necessary.

**MDR Reportable Complaints**

Section 820.198(c) specifically requires that any complaint involving the possible failure of a device, labeling, or packaging to meet its performance specifications shall be reviewed, evaluated, and investigated unless such investigation has already been performed for a similar complaint and another investigation is not necessary. Also, section 820.198(d) further specifies that any complaint that requires an MDR report shall be promptly reviewed, evaluated, and investigated by a designated individual(s), and shall be maintained in a separate portion of the complaint files or clearly identified. However, if maintained separately a manufacturer should duplicate these serious complaints in the regular complaint file to assure that any analysis performed by product is inclusive of all complaints. Analysis by appropriate statistical methodology where necessary is a means of identifying quality problems. A single event, of course, may also be an indicator of a quality problem.

**Complaint Records**

FDA does not specify a standard method for recording or retrieving complaint information. Each manufacturer should develop a method for maintaining records of complaints and investigations that: is functional and economical, meets company needs, and meets requirements of the Quality System regulation. A two sided form is suggested when using hard copy to record complaints. One side may be used to record complaint information such as:

- sequential number of the complaint;
- origin of the complaint;
- customer information;
- product information;
- any corrective actions already taken;
- details of the complaint;
- and dates, signatures, assignments, etc.

The other side may be used to record:

- instructions;
- investigations;
- analyses;
- conclusions;
- corrective action with respect to the product and to the customer;
- and dates, signatures, etc.
A typical form is exhibited at the end of this chapter. The completed form should be stored in the complaint file which may be a physical or electronic file.

**Investigation Records**

The designated unit or person(s) responsible for maintaining the complaint file(s) shall prepare a written record of any investigations. This record shall include [820.198(e)]:

1. The name of the device;
2. The date the complaint was received;
3. Any device identification(s) and control number(s) used;
4. The name, address, and phone number of the complainant;
5. The nature and details of the complaint;
6. The dates and results of the investigation;
7. Any corrective action taken; and
8. Any reply to the complainant.

Also, the investigation record of any complaint that is being reported to FDA in an MDR report shall include a determination of [820.198(e)]:

1. Whether the device failed to meet specifications;
2. Whether the device was being used for treatment or diagnosis; and
3. The relationship, if any, of the device to the reported incident or adverse event.

Section 820.198(e) requires the record of investigation to include any reply to the complainant. Manufacturers should send a reply to each complainant as a courtesy, but more important to prevent further misuse, injury or other adverse situations from recurring. However, because of the nature of the complaint, there may be cases where a reply is not necessary. In such cases, the record should state that no reply was made and the reason for not replying. When the problem was caused by misuse, it is very important to advise the user to help prevent further misuse. Also, the manufacturer should determine if inadequate labeling may have lead to misuse.

**File Accessibility and Location**

The GMP requirement states in 820.180 that "All records required by this part shall be maintained at the manufacturing establishment or other location that is
reasonably accessible to responsible officials of the manufacturer and to employees of the Food and Drug Administration designated to perform inspections." "All records" includes complaint files and records of investigations. For complaint processing, responsible officials are general managers, complaint processors, QA managers, R&D and process engineers, and others who receive, process, investigate, and correct problems associated with complaints. Complaint files shall be reasonably accessible to FDA for review and copying. FDA has clear authority under Section 704(e) of the Food, Drug, and Cosmetic Act to inspect and copy all records required under section 519 of this Act.

The GMP requirement states that complaint files must be handled by a formally designated complaint unit. If the unit or individual(s) designated as responsible for investigating complaints is located away from the actual manufacturing site, the investigated complaint(s) and the record(s) of investigation shall be reasonably accessible to the manufacturing site. If a manufacturer's formally designated complaint unit is located outside of the United States, records required by this section shall be reasonably accessible in the United States at a location in the United States where the manufacturer's records are regularly kept or at the location of the original distributor.

When devices are produced for a manufacturer by a contract manufacturer, the manufacturer should forward to the contractor copies of complaints and investigations that pertain to operations performed by the contractor. The contractor should maintain a complaint file and process complaints as discussed herein for the primary manufacturer.

Relabelers, importers, and others who distribute under their own name should forward complaints to the actual manufacturers, including foreign manufacturers, who are usually in the best position to resolve complaints on their own products.

Non-medical Complaints

 Certain manufacturers products may be used both as a medical device and for non-medical uses, for example lasers and motors. The complaints received from non-medical users do not necessarily have to be included in complaint files. However, if the non-medical product fails to meet specifications, then that report should be in the manufacturer's complaint file. This action would help assure compliance with 820.100, which requires identifying, recommending, or providing solutions for quality problems and verifying implementation of such solutions. The person receiving such complaints shall be trained [820.25(b)] to identify complaints that also affect those units used as medical devices.

Complaint Analysis

 To facilitate detection of failure or defect trends, complaint files should be arranged in a manner that permits correlating present and past complaints for a particular product or product line. Thus, files are usually organized according to product or product lines. Manufacturers who do not organize complaint files by product or product line may have to search several files to find similar complaints or indications to identify problem trends. Complaints may be maintained in a computer file so that complaint data on a specific device or type of complaint can be readily accessed and analyzed. As appropriate, complaint analysis or their summaries should be included in the management review and the quality system [820.20(c)].

DEVICE FAILURE ANALYSIS

 Manufacturers should process and analyze failed devices per 820.100. Section 820.100(a)(1) states that returned product is subject to corrective action. Failure analysis must be conducted by appropriately trained and experienced personnel [820.25(b)]. They should use a written procedure to assure that the process of device handling and analysis will not compromise the determination of the cause of the device failure. The failure investigation and analysis should determine the actual failure mechanism to the objective level necessary to correct the problem. When systematic failure has been diagnosed and corrective action established, a
manufacturer need not analyze all additional devices that are returned with the same symptoms.

If a failure is determined to be related to safety and effectiveness, the deficiency should be determined, corrected and documented. If an investigation verifies a particular device deficiency and that this deficiency may exist in other products, the investigation should extend to determining its effect on other medical products.

Any corrective or preventive action taken shall be done following the requirements in 820.100.

**FEEDBACK FOR QA SYSTEM**

The more comprehensive a quality system is, the lower the probability of complaints occurring. However, in order for a quality assurance system to be dynamic or self-correcting, data on quality problems from all sources should be fed back into the system. Complaints are a valuable source of data that can point to corrective actions.

Feedback data should flow into all operations that could be affected by the data and should be used to aid in device and process design evaluation and/or redesign, and to aid in improving the overall quality system program.

Regardless of the size of the formal quality system, the feedback data path in any company should be the same, that is, the data should flow into all affected operations even if some of these are not covered by the formal quality system or by FDA regulations.

**COMPLAINT SOURCES**

Complaints that shall be processed according to the GMP requirements may be received from:

- customers by letter, credit memo, returned goods form, or phone;
- a manufacturer's representative, or other employees;
- the MedWatch voluntary reporting program;
- a service or repair request;
- journal articles; or
- the FDA.

Complaints from any source shall be equally addressed by and be processed according to the company complaint policy and procedure. The company should make certain that market, sales, engineering, manufacturing, regulatory, installation, and service personnel are trained to properly identify and report complaints. These employees shall be made aware of this requirement according to section 820.25(b).

**MEDICAL DEVICE REPORTING**

In addition to the GMP requirements covering complaint handling and failure investigations, device manufacturers shall also comply with the Medical Device Reporting (MDR) regulation, 21 CFR Part 803.

**Who Must Report**
The MDR regulation requires that all manufacturers of medical devices notify FDA when they become aware of a death or serious injury that may have been caused or contributed to by one of their marketed devices and/or any malfunction of one of their devices which, if it were to recur, would be likely to cause or contribute to a death or serious injury. These are the same complaints that the Quality System regulation requires a manufacturer to place in a separate portion of the complaint file or otherwise clearly identify [820.198(d)]. The MDR regulation is intended to supplement the Quality System regulation -- it is not meant to replace the GMP complaint and failure investigation requirements.

**When to Report**

There are specific time limits within which the MDR reports shall be made. Any report of a device-related death, serious injury and malfunction shall be submitted within 30 calendar days from becoming aware of an MDR reportable event. To meet these requirements, manufacturers shall have an information handling system to assure that data are screened to determine what shall be reported to FDA. This system shall also be able to follow up this information quickly and accurately in order to comply with the MDR regulation. Manufacturers which have a good system for processing complaint and failure investigations such as described in this chapter will have the organization and data processing capabilities to meet the MDR requirements.

Manufacturers of medical devices are required to report a device related death, serious injury or malfunction to FDA using FDA Form 3500A, within 30 calendar days after becoming aware of the event. However, if the event necessitates remedial action to prevent an unreasonable risk of substantial harm to public health, then a report shall be submitted within 5 work days. Reports shall also be submitted when FDA notifies a manufacturer that 5-day reports involving a particular type of medical device or type of event are required.

The reporting process starts when an MDR reportable event is first recognized. Manufacturers are responsible for making sure their employees know how to recognize what may be reportable. Manufacturers should also emphasize that any employee may learn of an adverse event during a phone call, a sales visit, a professional conference, from correspondence received or from service/warranty orders.

**Individual Adverse Event Reports**

There are two types of individual adverse event reports that may be submitted by manufacturers. The 5 work day and 30 calendar day reports.

The 5-day report (803.53) is for MDR reportable event(s) that require a remedial action to prevent an unreasonable risk of substantial harm to the public health or where FDA has specified that a 5-day report is needed. This situation may be identified by the manufacturer or FDA:

- If the manufacturer identifies the event and initiates a remedial action to prevent an unreasonable risk of substantial harm to the public health, a 5-day report is submitted instead of the 30-day report. Information not available within the five days should be provided in a supplemental report.

- If FDA identifies the event, the manufacturer will receive a written request directing them to file a 5-day report for all subsequent events of the same nature that involve similar devices for a specified time period. The FDA identification may be a result of its review of 30-day reports, inspection reports, user facility reports, etc.

The 5-day period of reporting starts the day after any employee, who is a person with management or supervisory responsibilities over persons with regulatory, scientific, or technical responsibilities, or a person whose duties relate to the collection and reporting of adverse events, becomes aware that a reportable MDR event or events, from any information, including any analysis, necessitate remedial action to prevent an unreasonable risk of substantial harm to the public health.
The MDR regulation defines **remedial action** as any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a reportable event.

Not all remedial actions need to be submitted as 5-day reports. Only remedial actions that are necessary to prevent an unreasonable risk of substantial harm to the public health shall be submitted. If a remedial action is taken, **but it is not done to prevent an unreasonable risk of substantial harm to the public health** a 5-day report is not required. A 30-day report, however, may be required.

The discovery that a remedial action is necessary may be a direct result of one or more MDR reportable events occurring, or may be discovered through the performance of internal analyses using appropriate statistical or other acceptable methodologies for processing data.

Actions taken to fix a single device involved in the MDR reportable event are not remedial actions.

A 30-day report is required once a manufacturer receives or otherwise becomes aware of information that reasonably suggests that a device they have marketed:

1. has or may have caused or contributed to a death or serious injury; or
2. has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.

The 30-day period for reporting starts the day after receipt by any employee of information that reasonably suggests that an MDR reportable event has occurred. FDA expects manufacturers to train their employees to recognize that they have received information on an adverse event and to know to whom in the company to forward this information for an MDR evaluation.

A manufacturer is NOT required to file an MDR report:

- when it determines that a device related event did not occur, or
- when it determines that the device was made by another manufacturer.

For the latter instance, the regulation requires the manufacturer to forward whatever information they have to FDA with a cover letter explaining that they did not manufacture the device so that FDA can send it on to the correct manufacturer. In this case, a 3500A should not be completed. Manufacturers may also voluntarily send a copy of this information to the manufacturer they identify as being the actual manufacturer.

**Written MDR Procedures**

In addition to having general complaint handling procedures, the MDR regulation (803.17) requires manufacturers to develop, maintain and implement written MDR procedures that at a minimum:

A. Set up internal systems for:

- timely and effective identification, communication, and evaluation of any events that may be MDR reportable;
QSR Manual

- a standardized review process/procedure for determining when an event meets the criteria for reporting under the MDR regulation; and
- timely transmission of a complete MDR report to FDA.

B. Set up documentation and recordkeeping for:

- information that was evaluated to determine if an event was MDR reportable;
- all MDR reports and information submitted to FDA;
- any information that was evaluated when preparing the annual certification report; and
- systems that ensure access to information that facilitates timely follow up and inspection by FDA.

The MDR procedures should be either incorporated in the overall complaint handling procedure or be a companion to it. In either case these MDR procedures shall be clearly identified. If a companion procedure, it shall be incorporated by reference in the overall procedure. This will assure that all complaints are properly evaluated for MDR reporting.

Each manufacturer has certain discretion to determine the level of detail and depth of information that their written MDR procedures contain. FDA suggests that manufacturers provide policy and interpretation information regarding "typical" adverse events or product problems that may be MDR reportable. FDA also suggests that the procedures describe the investigation protocol that will be followed, e.g., two or three or four attempts will be made to contact the reporter either by phone, FAX or letter before an investigation is closed; that the complaint records will contain a concise but thorough description of the adverse event or product problem, that the complaint records will be legible, etc.

MDR Event Files

Each event that requires a determination regarding its MDR reportability shall be documented in an MDR event file (MEF) (803.18). This MEF will be one of the bases for establishing compliance with the requirements of the MDR regulation. Files are to be accessible to FDA personnel for review and evaluation, be as complete as possible, and are to clearly document MDR related actions and decisions. The following information should be in the MEF to assure that it complies with the MDR requirements:

a) The original or a copy of the initial record complaint/event. This record should include the available information needed to complete the Form FDA 3500A. The record may be documentation of a telephone call, a letter or facsimile, a service report, documents related to a lawsuit, a voluntary FDA 3500 received from a health care professional or consumer, or mandatory FDA 3500A received from a User Facility and/or a Distributor, etc.

b) Copies of any records documenting the manufacturer's attempts to follow-up and obtain missing or additional information about the event. When information cannot be obtained an explanation shall be made part of the file.

c) Copies of any test reports, laboratory reports, service records and reports, records of investigation, etc.
d) Copies of all documentation involving the final assessment of the event, any deliberations and/or decision making processes used to determine whether an MDR report was or was not needed. When applicable, the final assessment should indicate what action, if any, the manufacturer has taken to assure that the cause of the event is corrected or otherwise mitigated.

e) Copies of all FDA 3500A forms submitted to FDA, when applicable. This includes a copy of any FDA 3500A forms received from User Facilities and Distributors.

f) Documents verifying that the event has been evaluated in accordance with the applicable requirements of the QS regulation, sections 820.100 and 820.198.

g) References to any other relevant documents or information used during assessment.

**How To Maintain MDR Event Files**

The MEF can be written or electronic files. They may make reference to other information that was used during the investigational process, in lieu of copying and maintaining duplicates in the file. Any referenced material is to be made available to FDA personnel for review, copying and verification.

Each MEF shall be retained for a period of two (2) years from the date of the event or a period of time equivalent to the expected life of the device, whichever is greater. Each MEF file shall be maintained for this period of time even if the device is no longer sold/distributed by the manufacturer.

The MEF may be maintained as part of the complaint file required by 21 CFR Section 820.198, however, the MEF files shall be prominently identified.

**ADDITIONAL MDR GUIDANCE**

Manufacturers should refer to the guidance document entitled, "Medical Device Reporting for Manufacturers," for further information on how to comply with this requirement.

There is also a Web page devoted to MDR issues.

**REPORTS OF REMOVALS AND CORRECTIONS**

At the time of completion of this manual, FDA has not published a final rule implementing its authority under section 519(f) of the Act to require reports of removals and corrections. It is important to note, however, that the agency published a proposal to implement this authority at 59 FR 13828 (March 23, 1994). A final rule based on the proposed rule may require reporting different from or in addition to that required by the Quality System and MDR regulations.

**EXHIBITS**

Exhibits are described below which follow in the order described.

**Complaint Processing Procedure and Forms**
This sample procedure is used to establish and help implement a system for processing routine complaints for devices. The customer complaint form mentioned in the sample procedure is essentially the same as the form, "customer/device complaints," in the next exhibit. Nowadays the complaint log shown on sheet 3 of 5 is easily maintained on a computer.

An example of a complaint recording form follows the complaint processing procedure.

The form titled "Customer Complaint" can be used to record most complaints.

If it matches a manufacturer's needs, the complaint form may be used as is. Also, it may be modified to meet specific needs. If the form is modified or a new one is developed, a manufacturer should make sure the resulting form is consistent with the GMP requirements and consistent with any complaint handling policy and/or procedures being used at the manufacturer.

**MedWatch Forms**

A copy of the MedWatch 3500A is included at the end of this chapter. This form may be photocopied for submitting reports.

The MedWatch 3500A is also available from the Web page devoted to MDR issues.

*** SAMPLE PROCEDURE ***

<table>
<thead>
<tr>
<th>COMPANY LOGO</th>
<th>Sheet 1 of 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Complaint Processing Procedure</td>
</tr>
<tr>
<td><strong>Prepared by</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Approved by</strong></td>
<td></td>
</tr>
<tr>
<td><strong>ECN Notes</strong></td>
<td></td>
</tr>
</tbody>
</table>

**PURPOSE:** To establish and implement a procedure and forms for recording customer complaints, analysis, response, and corrective action. 

**POLICY:** It is the policy of our company that all complaints regarding safety, performance, or quality of our products or services will be subject to management review and/or investigation and will result in prompt response and corrective action where indicated.

**SCOPE / DEFINITION:** This policy is applicable to and must be complied with by all personnel who receive a customer complaint, including personnel in Sales and other departments.

A "complaint" is any indication of the failure of a device to meet customer or user expectations for quality or to meet performance specifications. Thus, any written, oral, or returned goods expression of dissatisfaction relative to the identity, quality, durability, reliability, safety, effectiveness, or performance of any device manufactured by this manufacturer would be considered a complaint.

Types of complaints intended to be covered by this policy are as follows:

**1. PRODUCT PERFORMANCE:** the product in some way does not perform to user's expectation or to any level of performance conveyed to the customer by printed labeling or verbally by company employees.
2. **PRODUCT SAFETY**: all safety complaints are covered by this procedure.

3. **PRODUCT RELIABILITY**: failure rate or need for service adjustments greater than user expectation, i.e. beyond the tolerable level of expected wear or malfunction.

4. **PRODUCT APPEARANCE**: visual defects inconsistent with the user's expectations for a medical device.

5. **GENERAL COMPLAINTS**: order or shipping error, delayed or unacceptable response to problems, unfulfilled promises, etc.

6. **MDR REPORTABLE COMPLAINTS**: all complaints involving device-related deaths, serious injuries and malfunctions. (See Policy/Procedure No. XXX for handling of MDR reports.)

**FORMS USED**: Customer/Device Complaint and Analysis and Complaint Log

**PROCEDURE**: Upon receipt of a customer complaint, the recipient completes side one of a CUSTOMER/DEVICE COMPLAINT form and, if the complaint is written, attaches the complaint letter to the form. The recipient then gives the form, with any attachments, by the next day to the Manager of Quality Assurance.

---

*** SAMPLE PROCEDURE Sheet 2 of 5

**IMPORTANT COMPANY POLICY**: Where a complaint requires immediate corrective action or response to a customer, the complaint recipient must either take the required action or communicate with the proper person to take the required action. It is the responsibility of the recipient of any complaint to see that the customer receives a response -- nothing in the following procedure relieves him or her of this responsibility.

**Quality Assurance**:

1. Assigns a sequential complaint number and enters the complaint into the Complaint Log.
2. Determines and notes on the complaint form the person to whom the complaint is to be assigned for investigation and/or corrective action and the date a response is required from the assignee.
3. Notes any specific instructions to the assignee.
4. Distributes a copy to appropriate Department(s) as checked on side 1 of the complaint form.
5. Makes 2 copies of all sides of the in-process form and attachments, and distributes:
   - Original to the Assignee.
   - One copy to the "UNDER INVESTIGATION" complaint folder.

The Assignee:

1. Performs the investigation and/or corrective actions and records the results on the form; and attaches any investigation records. If no investigation was done the reason why must be recorded and the name of the approving official documented.
2. Returns the original of the in-process form to QA.

**Quality Assurance**:

1. Records on the Analysis side:
   - If no action is taken, the reason for inaction should be recorded on the analysis form.
   - Any additional corrective action taken or directed by QA.
   - Whether an MDR report was submitted to the FDA.
   - The nature and date of any response made to the originator or the customer. If this response is written, a copy of the letter or FAX is attached to the analysis form.
   - The final disposition of the complaint.
   - QA signature and date.
QSR Manual

1. Distributes the complaint log monthly to Staff and specifically involved departments. This log should include a trend analysis of complaints for the month correlated with trends noted in previous months.

2. Records the final disposition of the complaint on the complaint log.

3. Files the completed form in the appropriate complaint file for the type of device involved; and discards the copy previously filed in the "UNDER INVESTIGATION" complaint folder.

*** SAMPLE RECORD ***

<table>
<thead>
<tr>
<th>COMPLAINT LOG</th>
<th>Sheet 3 of 5</th>
<th>MONTH, 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seq. No.</td>
<td>Date Rec'd.</td>
<td>Type Device</td>
</tr>
</tbody>
</table>

*** SAMPLE RECORD*** Sheet 4 of 5 of Procedure No. _________________

CUSTOMER COMPLAINT (Side 1) SEQUENTIAL NO. _________________

Device Name ____________________ Model Number ____________________
Catalog Number __________________ Lot Number ____________________
Distributor ____________________
Name of Complainant ________________ Phone No. ____________________
Complainant Address ____________________
Complaint Received by ____________________
Title ____________________ Date Received ____________________

By: Q Visit Q Phone Q Letter Q Sales Q Credit Memo Q Other ____________________

COMPLAINT ABOUT

Q Sterility
Q Particulate Matter Type ________________ Location ________________
Q Defect ____________________
Q Packaging ____________________
Q Labeling ____________________
Q Patient Death ____________________
Q Patient Injury ____________________
Q Product Malfunction ____________________
Q Other (specify) ____________________
Comments/Description of Event ____________________
ATTACHMENTS

Q Implicated Sample
Q Associated Sample
Q Letter

Received By QA Mgr ______________________________ Date __________________
Assigned To ___________________________________ Response Due _____________________________
Instructions ____________________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________

Distribution: Q Quality Control Q Engineering Q Production Q QA Q Sales Q Service

*** SAMPLE RECORD*** Sheet 5 of 5 of Procedure No. _________________

CUSTOMER ANALYSIS (Side 2) SEQUENTIAL NO. __________________________
Device Name ____________________________________ Model Number _____________________________
Catalog Number __________ Lot Number ____________ Date of Complaint Report _____________________
Name of Complainant ___________________________________________________________________________
Nature of Complaint _____________________________________________________________________________

ASSIGNEE EVALUATION
Date(s) Evaluation Performed______________________________________________________________________
Evaluation Results_______________________________________________________________________________
_____________________________________________________________________________________________
_____________________________________________________________________________________________

Q Copy of evaluation attached

CONCLUSIONS
Q Device Defective Q Device Failed to Meet Specifications Q Improper Use
Q Shipping Damage Q Repair Request
Q Other(specify) _______________________________________________________________________________

ACTION/REPLY TO COMPLAINANT

  ● None. Reason for no action __________________________________________________________________
  ● __________________________________________________________________________________________

Q Recalled. FDA phoned on - Date ______________ Spoke to ________________________________________
Q Complaint Committee Informed on - Date __________________ Q MDR Filed on - Date __________________
Q Referred to ______________________________ for Further Investigation or Correction
Q Replaced Q Repaired Q Credited Q Letter Sent Q Sales Follow Up
Q Reason for No Reply __________________________________________

NOTES:
FINAL DISPOSITION
Reviewed by: Quality Assurance ______________________________ Date ____________________
If requested: Engineering ______________________________ Date ____________________
Production ______________________________ Date ____________________
### A. Patient Information

1. Patient identifier
   - Age at time of event:
   - Date of birth:

2. Sex
   - Female
   - Male

3. Weight
   - lbs
   - kgs

### B. Adverse Event or Product Problem

1. Adverse event
2. Outcomes attributed to adverse event
   - Disability
   - Congenital anomaly
   - Life-threatening
   - Hospitalization - initial or prolonged

3. Date of event
4. Date of this report

### C. Suspect Medication(s)

1. Name
   - Give labeled strength & mfg/labeler, if known

2. Dose, frequency & route used
3. Therapy dates
   - if unknown, give duration

4. Diagnosis for use
5. Event abated after use stopped or dose reduced
   - Yes
   - No
   - Does not apply

6. Lot # (if known)
7. Exp. date (if known)

8. Event reappeared after reintroduction
   - Yes
   - No
   - Does not apply

9. NDC # - for product problems only (if known)

10. Concomitant medical products and therapy dates (exclude treatment of event)

### D. Suspect Medical Device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - Health professional
   - Lay user/patient
   - Other

5. Expiration date
6. Model #
7. If implanted, give date

8. If explanted, give date
9. Device available for evaluation?
   - Yes
   - No
   - Returned to manufacturer on

10. Concomitant medical products and therapy dates (exclude treatment of event)
E. Initial reporter

1. Name, address & phone #

2. Health professional?  
   - yes  
   - no

3. Occupation
   - blank

4. Initial reporter also sent report to FDA
   - yes  
   - no  
   - unk

F. For use by user facility/distributor/devices only

1. Check one
   - user facility
   - distributor

2. UF/Dist report number

3. User facility or distributor name/address

4. Contact person

5. Phone Number

6. Date user facility or distributor became aware of event
   - initial
   - follow-up #

7. Type of report event
   - death
   - serious injury
   - malfunction (see guidelines)
   - other

8. Date of this report
   - initial
   - follow-up #

9. Approximate age of device
   - patient
   - code
   - device
   - code

10. Event problem code (refer to coding manual)

H. Device manufacturers only

1. Type of reportable event
   - death
   - serious injury
   - malfunction (see guidelines)
   - other

2. If follow-up, what type?
   - correction
   - additional information
   - response to FDA request
   - device evaluation

3. Device evaluated by mfr?
   - not returned to mfr.
   - yes
   - evaluation summary attached
   - no (attach page to explain why not) or provide code.

4. Device manufacture date
   - initial
   - follow-up #

5. Labeled for single use?
   - yes  
   - no

6. Evaluation codes (refer to coding manual)
   - method
   - results
   - conclusions

7. If remedial action initiated, check type
   - recall
   - notification
   - repair
   - inspection
   - replace
   - patient monitoring
   - relabeling
   - modification/adjustment
   - other

8. Usage of device
   - initial use of device
   - reuse
   - unknown

9. If action reported to FDA under 21 USC 306(a), list correction/removal reporting number.

10. Additional manufacturer narrative
   - and/or

11. Corrected data
<table>
<thead>
<tr>
<th>4. Date received by manufacturer (month/day)</th>
<th>5. (A)NDA #</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IND #</td>
</tr>
<tr>
<td></td>
<td>PLA #</td>
</tr>
<tr>
<td></td>
<td>pre-1938</td>
</tr>
<tr>
<td></td>
<td>OTC product</td>
</tr>
</tbody>
</table>

(check all that apply)

- foreign
- study
- literature
- consumer
- health
- professional
- user facility
- company representative
- distributor
- other

| 6. If IND, protocol # |

<table>
<thead>
<tr>
<th>7. Type of report (check all that apply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-day</td>
</tr>
<tr>
<td>10-day</td>
</tr>
<tr>
<td>periodic</td>
</tr>
<tr>
<td>initial</td>
</tr>
<tr>
<td>follow-up #</td>
</tr>
</tbody>
</table>

| 8. Adverse event term(s) |

9. Mfr. report number

---

The public reporting burden for this collection of information has been estimated by the agency to average one hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and submitting the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to:

FDFA Form 3580A - back

Reports Clearance Officer, Paper Clearance Branch, Room 721-B
OCDE, FDA
2001 Rockville Pike
Bethesda, MD 20852-8279

Substitute: 1995-0281
Washington, DC 20500

Please do not return this form to either of these addresses.

Updated 1/1/1997
16. Servicing

INTRODUCTION
The requirements in the Quality System (QS) regulation govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. Servicing covers the maintenance and repair of finished, distributed devices.

The intent of the quality system regulation is to assure that servicing is correctly performed and verified according to company specified requirements such that the serviced device is suitable for the intended use and that service information is collected and analyzed to help correct any quality system problems and device design, manufacturing, labeling, or packaging problems.

The basic servicing requirements are in 820.200, Servicing. However, there are related requirements throughout the QS regulation. For example, service procedures are documented per 820.181, Device Master Record; and servicing activities and/or data may lead to complaint analysis per 820.198, Complaint Files, or require corrective and preventive action per 820.100.

When a finished device manufacturer contracts with another supplier to perform their servicing, such service (or service contractor) must meet the applicable purchasing and servicing requirements in the QS regulation.
Interfaces

There are interface requirements in the QS regulation that apply to service functions. Section 820.30(b), Design and Development Planning, requires that each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process.

The preamble clarifies the fact that these requirements extend to service functions by stating: the plan shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design process. Many organization functions, both inside and outside the design group, may contribute to the design process. For example, interfaces with marketing, purchasing, regulatory affairs, manufacturing, service groups, or information systems may be necessary during the design development phase. To function effectively, the design plan should establish the roles of these groups in the design process and describe the information that should be received and transmitted.

Therefore, for medical devices that require servicing, during appropriate activities such as design input and design reviews, service requirements and ease of service should be considered; and service managers, senior service technicians, etc., may need to participate in these design functions. Such participation may reduce the:

- need for maintenance and repairs;
- time to perform repairs,
- need for special tools; and
- cost of repairs.

Reducing the time for repairs and the need for special tools usually reduces production assembly time and manufacturing costs.

SERVICE PERSONNEL

Service shall be conducted by appropriately trained and experienced service personnel (820.25) in order to:

- assure, to the extent feasible, that the process of device handling, diagnosis, and repair will not compromise the determination of the root cause of the device failure;
- identify and correct the failure;
- correctly report the service information; and
- identify and report data related to a serious incident or adverse event.

The repair diagnosis should also try to determine, and/or provide adequate data to assist analysts in determining, the actual failure mechanism to the objective level necessary to correct or reduce the problem.

Thus, service personnel must be trained to adequately perform their assigned maintenance, repair, and reporting responsibilities. Such training shall be documented (820.25). The training is also performed in accordance with the instructions and procedures established under 820.200 for performing and verifying that servicing meets the specified requirements. Because servicing must be verified, service personnel must be made aware of defects and errors that may be encountered as part of their job functions (820.25). This training requirement usually does not require separate or additional training because basic training to perform repairs emphasizes the identification of defects and errors.

SERVICE REQUIREMENTS
The QS regulation does not require that a manufacturer service a device. The decision to service or have their devices serviced is left to the manufacturer. When a manufacturer specifies that they will perform service or contract to have service performed, such service must meet all of the applicable QS regulation requirements. Such a manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the manufacturers specified requirements. Section 820.200, Servicing, states:

(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.

(b) Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100.

(c) Each manufacturer who receives a service report that represents an event which requires reporting to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

(d) Service reports shall be documented and shall include:

1. The name of the device serviced;
2. Any device identification(s) and control number(s) used;
3. The date of service;
4. The individual(s) servicing the device;
5. The service performed; and
6. The test and inspection data.

INSTALLATION

Where service and installation are required by a manufacturer, both of these product activities are related and so are the QS requirements for both. Section 820.170 Installation states:

(a) Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device.

(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.

Some manufacturers use their service department or a service contractor to install their medical devices. Servicing may also include re-installing a device. As shown in Table 16.1, Comparison Of Servicing And Installation Requirements, the QS requirements for installation in 820.170 essentially parallel the requirements for service in section 820.200. For example, The QS regulation includes detail of the reporting requirements for servicing; for installation, the manufacturer chooses the information to document. However, from a practical viewpoint, each manufacturer would choose to have the
same information documented. Thus, as appropriate, a manufacturer may combine most of their service and installation QS activities.

**CONTRACT SERVICE**

When a finished device manufacturer contracts with another supplier to perform their servicing, such service (or service contractor) must be obtained per the applicable requirements in 820.50, Purchasing. Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received services conform to specified requirements. Each manufacturer shall establish and maintain the requirements, including quality requirements, that are to be met by contractors. Each manufacturer shall:

1. Evaluate and select potential contractors on the basis of their ability to meet specified requirements, including quality requirements. The evaluation shall be documented.

2. Define the type and extent of control to be exercised over the contractors based on the evaluation results.

3. Establish and maintain records of acceptable contractors.

Each manufacturer shall establish and maintain data that clearly describe or reference the specified service requirements, including quality requirements. Purchasing data shall be approved in accordance with 820.40.

A major portion of the purchasing requirements are met when the manufacturer meets the servicing requirements in section 820.200(a) which states:

(a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements....

That is, these specified requirements, service instructions and procedures, and device verification procedures may be used together with other information such as the finished device description to help show a prospective contractor the scope and expected quality of the servicing that is being contracted.

Table 16.1 **COMPARISON OF SERVICING AND INSTALLATION REQUIREMENTS**

<table>
<thead>
<tr>
<th>SERVICING</th>
<th>INSTALLATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) ... establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.</td>
<td>(a) ... establish and maintain adequate installation and inspection instructions, and where appropriate test procedures.</td>
</tr>
<tr>
<td>(a) ... and verifying that the servicing meets the specified requirements.</td>
<td>(a) Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation.</td>
</tr>
<tr>
<td></td>
<td>(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and ...</td>
</tr>
</tbody>
</table>
(b) Each manufacturer shall analyze service reports with appropriate statistical methodology in accordance with 820.100.

(a) ... establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements.

(b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.

(d) Service reports shall be documented and shall include:

1. The name of the device serviced;
2. Any device identification(s) and control number(s) used;
3. The date of service;
4. The individual(s) servicing the device;
5. The service performed; and
6. The test and inspection data.

(c) Each manufacturer who receives a service report that represents an event which requires reporting to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

## SERVICE EQUIPMENT

Section 820.20(b)(2) Resources requires each manufacturer to provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities to meet the requirements of this part. As appropriate, adequate resources include service instructions, service procedures, supporting DMR drawings, and service equipment. Service equipment includes equipment to perform the repair and to verify the proper performance of the serviced devices. Service equipment may include complex apparatus; however, it also includes any simple jigs, test cables, special hand tools, etc., as needed to meet the service needs of specific medical devices.

Servicing and Installation both require verifying that the device meets acceptance criteria. Therefore, appropriate and calibrated test equipment should be used. Section 820.72, Inspection, Measuring, and Test Equipment, requires that each manufacturer to ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained.

When establishing service and installation procedures, each manufacturer needs to comply with the Inspection, Measuring, and Test Equipment requirements, as appropriate, in order to assure that the serviced/installed device performs as intended. For example, a manufacturer may need to determine which service equipment, if any, needs to be calibrated in a laboratory and which, if any, may be calibrated using the self-contained internal calibrators. Also, the
manufacturer may need to select equipment that is capable of producing valid results after being subjected to repetitive and demanding service.

**SERVICE PROCEDURES**

If any are required, maintenance needs, schedules, and procedures are developed as part of the device design program. Some preventive maintenance tasks and their schedules may result from reliability studies performed during design development.

Repair procedures are based in part on design verification and finished device test and inspection procedures, production procedures, and rework procedures. Other aspects of repair procedures are developed by qualified technical personnel and senior repair technicians. The development of procedures may involve inserting failures or defects and having another person find and repair them. The problems, discovery methods, and rework techniques are documented.

For redesigns, existing maintenance and/or repair procedures that are known to be current and correct may be referenced in the new service procedures or these may be renumbered and copied into the new procedures.

Identifying defective subassemblies or modules in the device and replacing them with good modules is a common servicing practice. The defective assembly is discarded, sent to be investigated, or is repaired at a designated facility with the necessary environmental conditions and facilities; test equipment and tools; component availability; trained rework employees; etc. This approach should also be covered by appropriate procedures.

The development of service procedures includes the development of appropriate service reporting forms.

Service instructions and procedures must be documented per 820.40. They are part of the device master record (DMR). Typical DMR documents (820.181) that are needed for service or that may be modified for service include:

- device specifications including appropriate drawings, component specifications, and software specifications;
- quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used; and
- installation, maintenance, and **servicing** procedures and methods.

These DMR documents usually cover:

- what the device does;
- theory of operation;
- operating instructions;
- safety;
- device specifications;
- component specifications, identification, and nomenclature;
- test apparatus, jigs, and special tools;
- typical failure modes and conditions;
- how to identify and isolate failures;
- test points where specific parameters may be measured;
- removal and replacement of parts;
- testing and inspecting (verifying) the repaired device;
- re-installation procedures, if applicable; and
ACCEPTANCE STATUS

Each manufacturer shall identify by suitable means the acceptance status of devices to indicate whether it has been service and whether it conforms with the acceptance criteria. The conformance is determined by the procedures established in accordance with 820.200(a).

The identification of acceptance status shall be maintained throughout servicing of the device to ensure that only devices which have passed the required acceptance activities are distributed, used, or installed (820.86). Identification is usually done by appropriate information on a decal, tag, or an attached pouch that contains the service request and/or report.

If a decal is left on the serviced device, for the next request and service, the decal can provide immediate information about the last service date, etc.

SERVICE REPORTS

Service activities shall be documented by service personnel and sent to the manufacturer according to the manufacturer's established procedures. As mentioned, service reports shall include:

(1) the name of the device serviced;
(2) any device identification(s) and control number(s) used;
(3) the date of service;
(4) the individual(s) servicing the device;
(5) the service performed; and
(6) the test and inspection data.

The device identification should be specific regarding the revision level, modification version, software version, etc., of the device in order to support analysis of the service data.

The test and inspection data should verify that the servicing meets the manufacturer's specified requirements. That is, the serviced device did, or did not, meet the acceptance criteria. (See Acceptance Criteria below.)

The service reports should also include information such as:

- device owner, address and phone number;
- specific location of the device;
- any unusual environmental conditions;
- any evidence of damage or misuse;
- if the device failed to meet specifications;
- if the device was being used for treatment or diagnosis;
- relationship, if any, of device to a death or serious injury; and
- date of last service and service report number, if known.
SERVICE REPORT ANALYSIS

Each manufacturer that performs servicing shall analyze service reports with appropriate statistical methodology in accordance with 820.100, Corrective and Preventive Action, which requires manufacturers to establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for analyzing service records and other sources of quality data to identify existing and potential causes of nonconforming product or other quality problems. The primary intent is to identify the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems; and to verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.

Failure and service report analysis should be conducted by appropriately trained and experienced personnel (820.25). Such personnel are also one of the resource requirements in 820.20(b)(2).

The analysis of service reports or subsequent analysis of the same or equivalent device(s) should be designed to determine the actual failure mechanism or quality problem to the objective level necessary to correct the problem.

When systematic failure has been diagnosed and corrective action established, a manufacturer need not analyze all additional devices that are serviced or returned with the same symptoms.

The analysis of service reports is totally dependent on the quality of the data in the reports. Therefore, it is very important that service training cover reporting so that the resulting reports are correct, complete, understandable, and easy to analyze.

The service reports for routine service requests for maintenance, adjustment, or repair of damage or failure resulting from long use, misuse or accident, usually do not need the same level of analysis as for other failures. However, some requests for service may appear to be routine when, in fact, they may be for unusual conditions that warrant attention. For example, service requests because of rapid wear, unusual problems, unusual maintenance, or development of hazardous conditions should receive a complete analysis in order to determine if corrective action is needed in the preventive maintenance procedures, design, labeling, manufacturing processes, etc. Enough information should be obtained from the customer to determine whether the request is for routine maintenance or the device is to be serviced for other reasons.

Parts Shipping Trends

As appropriate manufacturers should periodically (e.g., monthly) examine shipping records for repair parts. Any increases in shipment of specific parts due to unknown reasons should be analyzed to determine if a significant failure problem exists. Manufacturers have identified quality problems by this simple, low-cost technique.

COMPLAINTS

Service requests for repairing or investigating an event that allegedly resulted in a death or serious injury shall also be investigated as a complaint. Section 820.200(c) requires that each manufacturer who receives a service report that represents an event which requires reporting [Medical Device Reporting (MDR)] to FDA under part 803 or 804 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198.

Section 820.198(d) requires that any complaint that represents an event which must be reported to FDA under part 803 or 804 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or otherwise clearly identified. In addition to the information
required by 820.198(e), records of investigation under this paragraph shall include a determination of:

(1) whether the device failed to meet specifications;

(2) whether the device was being used for treatment or diagnosis; and

(3) the relationship, if any, of the device to the reported incident or adverse event.

Because of the MDR and complaint relationship, manufacturers should have the service personnel collect as much as is possible of the information required to complete the records of investigation, steps 1 - 3 listed above. Thus, the service form for some devices may need blanks/areas to support the collection of the needed information.

The service requirements AND complaint requirements shall be met for such combination service/MDR/complaint events. If the death or serious injury was caused by a design error, it may not be possible to perform a repair.

CORRECTIVE AND PREVENTIVE ACTION

A major intent of the service requirements is to look for quality problems during servicing and analysis of service data, and, if problems are found that affect or could affect safety or performance, to mandate appropriate corrective action. Thus, the collection (820.200) and analysis (820.100) of servicing data are required and these are part of the quality feedback system. Without the feedback provided by the quality audit and other information sources, such as complaints and service records, manufacturers operate in an open loop system with no assurance that the process used to design and produce devices is operating in a state of control.

Section 820.100, Corrective and Preventive Action, requires the analysis of quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems.

In-warranty or out-of-warranty are not factors to be considered when collecting or analyzing data regarding servicing.

When nonconformities are found they are to be investigated to determine the cause, such as an inadequate quality system or a defect in the design, component(s), assembly, processing, labeling, packaging, installation method, service technique, etc.

The collection and analysis of service data should be broad based because the root cause may be: an inappropriate component; a bad component; early wear out; poor maintenance; compatibility; human factors, and safety; misuse; misuse due to inadequate labeling; poor workmanship; incorrect assembly; etc.

The investigation and corrective actions should continue until valid actions are identified and implemented to correct and prevent recurrence of nonconforming product and other quality problems.

If service instructions, techniques, equipment, etc., contribute to a quality problem, make a quality problem worse, destroy valuable data, etc., then such items are also subject to investigation and corrective action.

EXHIBIT

An example of a service request form is included in this chapter. This form may be modified to match individual needs as
CUSTOMER SERVICE REQUEST

Service Report No.:

Device Name:

ID/Cat. No.: Lot Number:

Any Specific Rev/Mod. #: Date placed in use:

Manufacturer/Distributor:

Account Name:

Account Address:

Phone Number: Fax Number:

Last Service Report (optional): Date Of Last Service:

Last service comments:

Technician: Date:

Device Location:

Customer Description Of Device Problem:

Were you told that there was a serious injury or death associated with this problem?

NO YES If yes, describe relationship to incident or event.

Was device being used for treatment or diagnosis?

Describe any unusual environment:

Describe any evidence of misuse:

If a repair, device problem(s) you found:

Maintenance and/or repairs performed:

Service Completed: Service not completed:

Reason Not Completed:

file:///C|/Documents%20and%20Settings/HP_Administrato...sktop/Linked%20Files/Design_Controls/QSR/16servg.html (10 of 11)6/13/2005 7:48:57 PM
CUSTOMER SERVICE REQUEST

In charts below, write identification code of components replaced. Write in first letter of ID code where necessary. Be **SURE** to put drawing number & rev. level in top row.

<table>
<thead>
<tr>
<th>Drawing number that shows replaced components listed below: rev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP</td>
</tr>
<tr>
<td>RES</td>
</tr>
<tr>
<td>IC</td>
</tr>
<tr>
<td>TRANSISTOR</td>
</tr>
<tr>
<td>DIODE</td>
</tr>
<tr>
<td>BAT</td>
</tr>
<tr>
<td>FUSE</td>
</tr>
<tr>
<td>CABLE</td>
</tr>
</tbody>
</table>

Updated 1/1/1997
17 QUALITY SYSTEM AUDITS

INTRODUCTION

Section 820.20 outlines the quality system requirements of the Quality System (QS) regulation. As discussed in Chapter 2, every quality system should include: management policies; objectives; an organization; documentation; performance of tasks according to policies; monitoring of the system (feedback) and corrective action as indicated by the feedback. Section 820.22 requires that the quality system be monitored through audits. The analysis and use of feedback data from product acceptance, audits, complaints, repairs, and other sources are necessary parts of a self correcting quality system. Thus, the audit of a quality system is one of the most important GMP requirements. The quality system first implemented by a new manufacturer will change as the manufacturer grows and as the company=s products, operations and employees change. Therefore, a quality system should change with the company. Quality system audits are the primary tool for assuring that the quality system changes are correct and are correctly implemented.

A quality audit is a documented independent inspection and review of a quality system. The audit is...
performed on a periodic basis in accordance with written procedures. The objective is to verify, by
examination and evaluation of objective evidence, the actual degree of compliance with those elements
of the quality system under review. These audits are an essential part of every medical device
manufacturer's effort to assure safe and effective devices. Regardless of how well a quality system is
planned, monitoring of the system is required if the quality system program is to be effective in assuring
that finished devices meet specifications. FDA analysis of factory inspections has shown that
manufacturers who do not have an adequate quality audit system usually do not have an adequate quality
system. An evaluation of approximately 2400 manufacturers that had received GMP inspections by FDA
showed that manufacturers with an adequate quality audit system were in compliance with
approximately 96 percent of the GMP requirements, while those that did not have an adequate audit
system were in compliance with approximately 70 percent of the requirements.

If conducted properly, a quality audit can detect quality system defects. Isolation of unsatisfactory trends
and correction of factors that cause defective products prevent the production of unsafe or
nonconforming devices. Without an effective quality audit function, the quality system program is
incomplete -- there is no assurance that a manufacturer is consistently in a state-of-control. In addition,
the proper implementation of a quality audit system can result in cost savings by identifying and
correcting problem areas. Without an audit, the quality system becomes an open loop without feedback
to management and without corrective action. Without overt management support, the quality system
program will eventually become ineffective and, as history has shown, ignored.

AUDIT REQUIREMENTS

The QS regulation requires that planned and periodic audits of the quality system shall be performed to
verify compliance with the quality system requirements. The audits are to be performed in accordance
with written procedures by appropriately trained individuals who do not have direct responsibility for
the matters being audited. Audit results shall be documented in written audit reports, which shall be
reviewed by management personnel, who have responsibility for the matters audited, and by other
involved parties. Follow-up corrective action, including re-audit of deficient matters, shall be taken
when indicated. Upon request of a designated FDA employee, an employee in management with
executive responsibility shall certify in writing that the audits have been performed and documented, the
dates on which they were performed, and that any required corrective action has been undertaken.

To assure that company quality goals will be routinely met and to comply with the QS regulation,
quality system audits should:

- measure the effectiveness of the quality system;
- provide objective evidence that adequate controls are in place; and
- assure that products and processes conform with specifications.

Where practical, manufacturers should include audits of their suppliers, calibration laboratories, and
contractors as part of a quality system audit. Manufacturers should audit suppliers where needed, to
assure that they have adequate quality system controls for raw materials and components shipped to and received by the manufacturers under supplier certification or certificate of compliance with specifications. An example of a detailed supplier (vendor) survey (audit checklist) form is in the Exhibits.

**Procedure**

All manufacturers should have a written quality audit procedure, although the details will vary with the manufacturer size and nature of the manufacturing operations. An audit procedure should include:

- an objective,
- audit scope,
- an audit schedule,
- assignment of responsibilities,
- evaluation criteria,
- management review of results, and
- corrective action policies, schedules, etc.

Before writing their audit procedure, some manufacturers may find it helpful to rearrange the key GMP requirements for an audit in a structured format as shown below:

- **Who?** Designee(s)
- **What?** Quality system
- **When?** X months
- **How?** Per checklist
- **Results?** Report/review
- **Actions?** Corrective

This structured format helps lead auditors into covering key requirements in the audit procedure and "getting straight to the point when writing procedures." Thus, this format tends to reduce the length and increase the clarity of audit procedures.

Formal procedures should start with an objective. In this case, the audit objective was discussed in the opening paragraphs of this chapter -- to monitor the quality system and take any needed corrective action. The audit scope should include all functions that impact on whether devices will meet specifications. These functions include personnel training, facilities, environment, design controls, device master and history records, equipment calibration, suppliers, label control, process controls and validation, complaint files, data feedback, preparation for FDA GMP inspections, etc. Manufacturers that have a total quality system composed of a design quality system and a manufacturing quality system should audit the entire system; otherwise, it is no longer a total quality system! Audits should cover all buildings and operations as necessary to make certain that the desired or required quality system is properly implemented.
The quality system audit required by the QS regulation is not intended to be a product audit. However, the adequacy of procedures used to determine product acceptability should be audited periodically. Product audits and review of the device master record are desirable as independent evaluations of product quality to determine the product's fitness for use and conformance to specification and, these may be acceptable in satisfying most quality audit requirements when product and process are very simple and the operation is small. As products and processes become more complex, evidence from inspection and testing of products no longer provides full assurance that the manufacturing system will consistently produce quality products. Instead, full quality system audits are required to make certain that:

- the established quality system is adequate for producing devices that consistently meet the device master record requirements,
- all system requirements are being met, and
- the system will continue to function when new products are introduced, changes are made, the workforce is understaffed, and the manager is on vacation.

**Audit Schedule**

Manufacturers are responsible for deciding the frequency of audits. The frequency should depend upon previous audit findings, any indications of problems, and known stability of the manufacturing process. If an audit reveals no problems, the audit intervals could be lengthened -- if problems are identified, audits may need to be conducted more often. Audits are usually conducted every 6 to 12 months, but should not exceed 12 months. Some companies split their audit into parts, and perform one or more parts per month or quarter, or audit one or more operations per month or quarter. This approach is valuable because it tends to direct attention toward problems that can be resolved within reasonable time limits and existing budgets. However, such segmented audits may fail to identify company-wide problems. Thus, reviewers of segmented audit reports should look for indications of company-wide problems.

**Independent Auditor**

The QS regulation (820.22) requires that quality system audits be conducted by individuals not having direct responsibility for the matters being audited. This requirement may be satisfied by an audit team consisting of persons representing product development and manufacturing. Then, when the product development area is being audited, the manufacturing persons should have the lead responsibility and vice versa. For any element of the quality system being audited, at least one member of the team should not have direct responsibility for the element being audited. Management should designate one member as the team leader for a given audit in order to support consistency, timeliness, completeness, and uniform response. Of course, a consultant, corporate, or other independent auditor may be used.
The requirement for an independent audit should generally be met; however, if a very small manufacturer, particularly one in which everyone is directly involved in daily design and production activities, concludes that independent audits would be unduly burdensome or impractical, the requirement for independence may be waived. However, if FDA finds, as a result of inspection or other means, this waiver has compromised the quality system, FDA may require an independent audit, increase the frequency of FDA GMP inspections, or take other appropriate regulatory action.

**Employee Training**

Individual(s) responsible for conducting audits should be sufficiently trained and experienced to detect variations and problems in the quality system [820.20(b), 820.22]. An auditor is expected to objectively compare existing employee training, design controls, manufacturing processes, facilities, environmental control, records, test/inspection activities, label control systems, feedback, etc., against what they should be. To do this, the individual(s) should have a working knowledge of:

- how products are developed and validated,
- how the device(s) is made,
- the manufacturing processes and process controls,
- how changes are controlled,
- quality assurance principles that apply, and
- the human relations aspect of auditing.

As with any GMP training, a record shall be maintained of the audit training given each employee.

Because the quality system requires a written audit report, auditors should have sufficient writing skills to effectively communicate findings and recommendations. The effectiveness of the audit begins with the planning. The manufacturer should start by defining the purpose and scope of their audit keeping in mind their quality systems requirements. An audit team leader and the other members of this team should be identified early in the planning process. The members of this team should possess skill and knowledge of quality system principles. Preparing an audit checklist will enable the team to properly cover the quality system requirements. Review of previous audits and their resulting reports is an excellent way for the audit team to correctly evaluate their quality system audit program. The background preparation should also include becoming familiar with company policies, operations, and products. The audit team should notify the parties they will audit and also hold a pre-audit conference among the audit team members to clarify exactly what the audit will include and what the objective(s) of their audit will be. Thus, preparing for an audit should include elements such as:

- selecting a knowledgeable audit team,
- preparing an audit checklist,
- developing a planned and systematic procedure,
- structuring the audit to determine both positive and negative trends, and
- structuring the audit and report to promote follow-up actions.
Evaluation Criteria

Each manufacturer shall determine the criteria to be used for conducting the audit. In general, medium to large manufacturers will need extensive documentation outlining the areas to be audited and the acceptable criteria for each of these areas. The GMP requirements are a baseline for the evaluation criteria; however, because the QS regulation is broad, each manufacturer shall tailor the criteria to the design and manufacturing operations they are actually performing. Small manufacturers may need only minimal documentation, and this may consist of an audit checklist with appropriate ancillary instructions to assure that all aspects of the quality system are covered.

An audit checklist may be a series of questions, phrases, trigger words, or any combination of these that will prompt auditors to cover the entire quality system. Checklists should cover requirements of the QS regulation applicable to company products, operations, and other areas company management has decided are included in their total quality system. If operations or devices change, evaluation criteria and checklists shall be appropriately updated.

Results and Corrective Actions

A quality system audit program that has been established in accordance with the QS regulation and implemented in sufficient depth can detect undesirable variations and trends in operating procedures. Management awareness of these undesirable variations should lead to corrections and help prevent the design and production of unsafe, unreliable, or ineffective devices.

The QS regulation requires follow-up corrective action, including re-audit. When indicated, audit results shall be given to individuals responsible for each of the operations audited, especially if deficiencies are found. Audit results shall be reviewed by all key management personnel, especially those responsible for the matters audited.

An audit should never be used as a disciplinary tool. This use will lead to ineffective audits because employees may become reluctant to reveal any possible problems for fear of retribution.

Audit Certification

Under 704(e) of the FD and C Act FDA has authority to review and copy all records required by the QS regulation; however, FDA has elected not to review audit reports. The exception [820.180(c)] to FDA's policy of not seeking access to reports of audits of quality systems is that FDA may seek production of these reports in litigation under applicable procedural rules, along with other confidential documents. Thus, a copy of the current audit report should be maintained by the manufacturer. FDA policy was established because the agency does not wish to prejudice audits by having auditors concerned that their comments will be reviewed by FDA investigators. Although FDA investigators do not have routine access to audit reports, they can request manufacturers to certify that audits have been conducted and the results documented; however, investigators do not routinely request certification. If requested, an
employee in management with executive responsibility should certify, in writing, that the manufacturer has complied with the audit requirements of the QS regulation.

Investigators usually will ask questions regarding the audit report such as:

- who prepared the report;
- what does the quality system audit include;
- when was the report written;
- using the checklist how should the audit be conducted;
- who reviewed the information and wrote the report; and
- were corrective action and re-audit(s) taken based on the audit result.

If investigators suspect audits are not being conducted, questions to determine consistency in answers may be addressed to those individuals who should have reviewed these reports. FDA investigators will routinely review audit procedures and audit checklists.

EXHIBITS

Two examples of audit procedures with checklists are included in this chapter. These may be modified to match individual operations as appropriate or used as guidances.

Policy/Procedure for Quality System Audit

In response to requests by small manufacturers, DSMA developed this procedure as an example of a minimum procedure for quality system audits. Following the procedure are comments to aid small manufacturers in completing the procedure and developing a checklist that should be used with it.

No details are given for the format of the audit "report" because the format generally is not important for the small manufacturer -- employees of small manufacturers communicate daily with each other. In fact, the "report" may be the list of findings neatly noted on the audit checklist. As noted in the procedure, however, summaries of the audit findings and corrective actions are recommended. The format Who, When, etc. discussed in the text, was used to develop this example procedure. The first three items in this format are reflected in item 1 of the example and the remaining three are reflected in items 2, 3 and 4 of the example. The scope encompasses the entire quality system.

Quality System Audit Procedure

Quality System Audit Procedure is an audit procedure that can be used by a medium to large manufacturer. In comparison to the small company, there are more people on the audit team, more audits per year, and the reports are distributed to more managers, some of which may be at corporate headquarters. Therefore, this procedure contains more details than the one suggested for the small company. For example, the procedure dictates the format of the audit report for the benefit of the
managers, who may review reports for many different operations per year.

**Vendor Survey Form**

The vendor survey form is applicable to a vendor or contractor or may be modified and used as an internal audit checklist. This survey form is divided into areas of concern such as raw material and component control, manufacturing, quality control/assurance, etc. Also, it is a more conventional checklist with places to check off answers to the questions. This form includes a header with space for manufacturer name, address, date prepared, etc., and general information about the manufacturer such as annual sales, years in business, other plant locations, etc. Your manufacturers can look at these two styles of checklists and decide to use one or the other, a combination of both, or a totally different format.

---

Title: **POLICY/PROCEDURE FOR QUALITY SYSTEM AUDIT** No. _____ Rev. ______

Approved by_____________________________________Date______________________________

1. A general audit of the entire quality system shall be performed by_______________________
every______ months (an audit team may be used).

2. The latest company approved audit checklist (number) _________shall be used. The audit checklist
shall be updated as required and approved by __________________________to reflect our current
quality system needs.

3. The completed checklist and audit results summary report shall be reviewed with the following
managers, as appropriate, who are responsible for the matters audited: ____________________,
_______________________________________and___________________________________.
Minutes of the review meeting, including a list of attendees and desired corrective actions, shall be
taken, distributed and filed by_______________________________. This same procedure shall be
used when reviewing the findings of GMP inspections by FDA investigators. (820.20)

4. Corrective actions shall be taken by all affected persons as discussed in the review meeting.
_____________________________will coordinate the corrective actions, re-audits, and keep
management informed. A summary report of the status of the corrective actions, as determined by a re-
audit of the affected areas or other appropriate means, will be written by _______________________
and filed with the original audit report. The status report shall be updated at least bimonthly if there are
any uncompleted corrective actions.
Comments on the Policy/Procedure

A. "Rev." is the revision level of the latest company approved procedure.

B. The above blanks should be completed with employee position titles and, if desired, employee names.

C. An audit checklist may be a detailed series of questions, phrases, trigger words or any combination of these to assure that the auditor covers the entire quality system. The checklist should cover the requirements of the QS regulation applicable to each company's products and operations plus other areas that company management had decided are included in the total quality system. A suggested way to develop a question-type checklist is to refer to the table of contents of the QS regulation and the chapters of this manual. Then generate questions for each topic as applicable to specific products and operations of the manufacturer. If operations or devices change, the checklist should be updated. A small portion of a quality audit checklist follows.

Sheet 2 of 6

A few cites are given. There are more. For example most of the QS regulation applies to labeling -- not just 820.120.

**SPECIFICATION CONTROLS** (820.30, .40, and .181)  YES  NO  COMMENTS

1. Is an adequate system in place to control all engineering drawings, specifications and other related documentation?

2. Does the system require adequate review, and approval of all new documentation and changes to documents?

3. Does the system require controlled, timely distribution of new specifications and specification changes?

4. Are procedures provided and adequately implemented to assure collection of obsolete documentation?

5. Are all specifications used in production
PROCESS CONTROLS  (820.70, .40, .60 and .80, .86)  

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Are current, approved process specifications/procedures such as work instruction, etc., used to define each process?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Are process changes made according to a formal change system and documented?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Are process changes communicated in a timely manner?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Do process specifications and procedures properly reflect the work to be accomplished?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>Are adequate acceptance and rejection criteria provided for the output of each process?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Are in-process and rejected items adequately identified and/or segregated to prevent mix-ups?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PERSONNEL  820.20(b)(2), 820.25, and 820.70(d)  

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Are there sufficient personnel having the necessary education, background, training, and experience to assure that all design and manufacturing operations are correctly performed?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Are training programs conducted and documented? Is the program proactive? Do design personnel have basic training in safety, use of standards, labeling, and applicable regulations?

3. Are all employees made aware of device defects which may occur from the improper performance of their specific jobs?

4. Are all employees including salespersons made aware that they must report all complaints received from any source to the company complaint department?

5. Are quality system personnel made aware of defects and errors likely to be encountered as part of their individual quality system function?

6. Are verification/validation personnel made aware of design errors that may be found?

7. Are personnel in contact with the device or its environment appropriately:
   a. clean?
   b. healthy?
   c. attired?

8. Etc.

<table>
<thead>
<tr>
<th>QUALITY ASSURANCE FUNCTIONS</th>
<th>YES</th>
<th>NO</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the quality assurance unit or qualified designee do the following?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. review customer purchase orders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. approve or reject components</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. approve or reject manufacturing materials</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
d. approve or reject in-process materials
e. approve or reject packaging materials
f. approve or reject labeling
g. approve or reject finished devices
h. approve or reject devices manufactured by another company
i. review production records
j. approve or reject devices processed by another company
k. approve or reject devices packaged by another company
l. approve or reject devices held under contract by another company
m. help provide solutions for quality system problems
n. verify implementation of solutions for quality system problems
o. assure that all quality system checks are appropriate and adequate
p. assure that all quality system checks are performed correctly

2. Are periodic audits of the quality system conducted to verify compliance with quality system program requirements?

3. Are audits of the quality system program:
   a. performed in accordance with written procedures?
   b. conducted by appropriately trained individuals?
   c. conducted by individuals who do not have direct responsibility for matters being audited?

4. Are audit results:
   a. documented in written audit reports?
b. reviewed by management having responsibility for the matters audited?

5. Does company have a copy of the last audit report on file?

6. Is follow-up corrective action, including re-audit of deficient areas, taken when indicated?

7. Etc.

QUALITY SYSTEM AUDIT PROCEDURE

Sheet 1 of 3

No._______ Rev._____ Approved___________________________________ Date _____________

ECN History____________________________________________________________________
_________________________________________________________________________________

POLICY: Periodic and planned audits of systems, training documentation processes, product flow and feedback shall be performed to assure compliance with regulatory and company requirements for current Good Manufacturing Practices (quality system).

SCOPE: All facilities, design activities, manufacturing operations, and product lines.

PROCEDURAL GUIDE: An audit of design activities shall be done annually. Routine quality audits of selected production areas shall be conducted each month. The entire operation shall be covered during a 12-month cycle. An area may be audited more than once. An "Action Audit" for any area or element may be initiated by the Manager of Quality Assurance at any time if a special problem arises.

The teamwork approach shall be used to identify and correct deficiencies.

The audit team shall consist of the Senior Quality Auditor (team leader) plus one or more individuals from other disciplines who have no direct responsibility for the area being audited. A team auditing an Operations unit should include an R&D representative. A team auditing a quality systems unit should include an Operations representative. An audit of design activities shall include a representative from both the regulatory and the manufacturing divisions.
The Manager of Quality Assurance selects the team member in consultation with the Department Managers.

A. AUDIT PREPARATION - The Quality Auditor (team leader) reviews applicable change control records subsequent to a design transfer, any FDA clearance delay information, recall records, standard manufacturing procedures, device histories, complaint history, device labels and inserts, previous audits with results, follow-up audits, plus any other document relative to the audit.

B. AUDIT INITIATION - The Quality Auditor prepares/updates an audit checklist for systematic examination of the area to be audited, informs the Manager of the department being audited at the start of the audit, and reviews observations with the Department Manager.

C. AUDIT ANALYSIS - The Quality Auditor reviews the data gathered, verifies important details, and writes an audit report according to the format delineated in the attached audit report outline.

D. ISSUANCE OF AUDIT REPORT - The Quality Auditor issues the written audit report to the President and Department managers within three working days following completion of the audit. If conditions are critical, the Director of Quality Assurance shall verbally brief appropriate staff members within 12 hours following audit completion. Audit reports shall be stamped "Confidential".

E. CORRECTIVE ACTION - The appropriate Management staff member shall be responsible for developing a schedule for correcting deficiencies cited in the audit report and submitting same within five working days to the Quality Assurance Manager. Included in the correction schedule shall be the responsible individual, and the date when corrective action will be completed. The Manager of Quality Assurance shall act as arbiter, if necessary, to judge validity of the deficiency, responsible individual, and reasonable date to complete the corrective action.

F. AUDIT FOLLOW-UP - The Quality Auditor maintains a log listing deficiencies, responsible individual, target date for corrective action, and actual date of correction. If the same deficiency occurs on a second follow-up audit, the President shall be notified in writing by the Quality Assurance Manager.

G. LOG OF AUDITS AND FOLLOW-UP AUDITS - The master log shall be maintained by the Senior Quality Auditor. The audit log file shall include a copy of current audits, list of areas to be audited during the 12-month period, and list of areas audited to date (i.e., part of the Master Log).

H. REPORT NUMBERS - Audit numbers shall be composed of the date followed by the sequential
number of the audit being reported (e.g., 98-4 for the 4th audit during 1998).

AUDIT REPORT COVER DATA

Area Audited ____________________________ Audit No._____________ Date: ____________

Audit Team members________________________________________________________________
_________________________________________________________________________________

Sr. Auditor's Signature: ___________________________________________________ (Team Leader)

REPORT OUTLINE

1. PURPOSE AND AREA DESCRIPTION - Describe initiating factors for the audit, limitations of audit, and area being audited.

2. MAJOR FACTS - Summarize for management review the most undesirable conditions and practices in order of their relative importance.

3. OBSERVATIONS AND FACTUAL DETAILS - Give a detailed account of the current practices and the deficiencies listed in four below.

4. DEFICIENCIES - List deficiencies in procedures, standards, documentation, safety, etc., along with identity of relevant regulation, SMP, SOP, etc.

5. FOLLOW-UP - State plans for follow-up review to establish individual responsibilities and completion dates.
# VENDOR SURVEY FORM

**DATE PREPARED**

**NOTICE:**

I (We) certify that the information contained in the attached survey form is accurate and complete as of the date indicated. Where trade secret or other proprietary information is involved, the person interviewed has waived those responses not verified by the interviewer. All information obtained will be kept confidential. A corporate officer of the company surveyed will review all responses made at the time of survey. This survey has been made with the permission of the company surveyed.

<table>
<thead>
<tr>
<th>SIGNATURE</th>
<th>TITLE</th>
<th>LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNATURE</th>
<th>TITLE</th>
<th>LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SIGNATURE</th>
<th>TITLE</th>
<th>LOCATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## PART I — GENERAL INFORMATION

**TOTAL NUMBER EMPLOYEES:** ________  **LABOR RATIO OF SUPERVISORS:** ________ TO **PRODUCTION PERSONNEL:** ________

**WORK SCHEDULE HOURS:** ________  **NUMBERhifts:** ________  **DAYS PER WEEK:** ________

**ARE TRAINING PROGRAMS FOR PERSONNEL UTILIZED:**

- [ ] Yes
- [ ] No

**FACILITY**

- [ ] Single/Multi-story
- [ ] Wood
- [ ] Brick
- [ ] Block
- [ ] Steel

**NUMBER BUILDINGS ON SITE:** ________

- [ ] Industrial Park
- [ ] Urban
- [ ] Suburban
- [ ] Rural
- [ ] Equipment owned or leased

**LOCATION IN MANUFACTURING:** ________  **Administration:** ________  **Storage:** ________  **Engineering:** ________

**SQUARE FOOTAGE:**

- [ ] Manufacturing
- [ ] Administration
- [ ] Storage
- [ ] Engineering, R&D

---

17-17
## Part II — Raw Materials and Components Control

### Purchasing
- Is qualification based on written specifications and approval of vendor sources? Yes □ No □
- Are reject/accept limits shown? Yes □ No □
- Is approval based on quality history cards? Yes □ No □
- Are suppliers' certificates obtained on site? Yes □ No □
- Use own QC testing? Yes □ No □

### Other
- Are specification changes reviewed and signed off by QC personnel? Yes □ No □

### Testing
- Are written test procedures in use? Yes □ No □
- Test results on file? Yes □ No □
- Sampling plan used? 100% □ SPEC □ AQL □ RANDOM □

### Other

### Part III — Manufacturing

### Master Production Records
- Is there a single controlled file of master records for each product? Yes □ No □

### Other
- Are these master records signed and dated? Yes □ No □
- Are the process, assembly, or manufacturing steps fully described? Yes □ No □
- In the master production record? Yes □ No □
- In a separate document or record? Yes □ No □
<table>
<thead>
<tr>
<th>QSR Manual</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS THERE A MASTER DOCUMENT TO INDICATE:</td>
</tr>
<tr>
<td>QC POINTS FOR IN-PROCESS MANUFACTURING</td>
</tr>
<tr>
<td>TYPE OF TEST OR INSPECTION TO BE MADE</td>
</tr>
<tr>
<td>METHOD OF MEASUREMENT</td>
</tr>
<tr>
<td>WHO PERFORMS TEST OR INSPECTION</td>
</tr>
<tr>
<td>LEVEL OF ACCEPT/REJECT (LIMITS)</td>
</tr>
<tr>
<td>FOR MANUFACTURING, PROCESSING, SUBASSEMBLY, OR PACKAGING DONE BY OUTSIDE SOURCES, ARE THERE MASTER PRODUCTION RECORDS</td>
</tr>
<tr>
<td>QC SPECIFICATIONS AND METHODS RECORDS</td>
</tr>
<tr>
<td>OUTSIDE SOURCES NOT USED</td>
</tr>
<tr>
<td>PRODUCTION AREA</td>
</tr>
<tr>
<td>IS THE WORK FLOW ORGANIZED</td>
</tr>
<tr>
<td>DISTINCT STAGING AREA FOR RAW MATERIALS OR COMPONENTS USED IN MANUFACTURING</td>
</tr>
<tr>
<td>PRODUCTION OR ASSEMBLY LINES SEgregated</td>
</tr>
<tr>
<td>GENERAL HOUSEKEEPING AND ENVIRONMENTAL FACTORS GOOD</td>
</tr>
<tr>
<td>WRITTEN PROCEDURES FOR PLANT SANITATION AVAILABLE</td>
</tr>
<tr>
<td>PRODUCTION EQUIPMENT</td>
</tr>
<tr>
<td>MAINTENANCE OR SERVICE RECORDS AVAILABLE</td>
</tr>
<tr>
<td>CALIBRATION RECORDS KEPT ON PERIODIC BASIS</td>
</tr>
<tr>
<td>MEANS OF READILY IDENTIFYING TYPE AND STAGE OF PROCESSING BEEN DONE ON THE EQUIPMENT</td>
</tr>
<tr>
<td>PRODUCTION RECORDS</td>
</tr>
<tr>
<td>ARE PRODUCTION DOCUMENTS COLLECTED AND FILED</td>
</tr>
<tr>
<td>Kept _______ (YEARS)</td>
</tr>
<tr>
<td>COMPLETE LABELING SAMPLES HISTORY INCLUDED TRADEABILITY BY LOT OR SERIAL NUMBER</td>
</tr>
<tr>
<td>PART IV - QUALITY CONTROL/ASSURANCE</td>
</tr>
<tr>
<td>DOES THE QUALITY CONTROL/INSPECTION GROUP HAVE FULL AUTHORITY TO HEDULE A BUDGET OR OPERATE INDEPENDENTLY</td>
</tr>
<tr>
<td>TO MANUFACTURE, REWORK, OR REJECT A PRODUCT</td>
</tr>
<tr>
<td>PACKAGING</td>
</tr>
<tr>
<td>ARE FINISHED GOODS PACKAGING OPERATIONS SEgregated UNDER SUPERVISED CONTROL</td>
</tr>
<tr>
<td>LABEL RECORDS KEPT</td>
</tr>
<tr>
<td>PART IV - QUALITY CONTROL/ASSURANCE</td>
</tr>
<tr>
<td>DOES THE QUALITY CONTROL/INSPECTION GROUP HAVE FULL AUTHORITY TO HEDULE A BUDGET OR OPERATE INDEPENDENTLY</td>
</tr>
<tr>
<td>TO MANUFACTURE, REWORK, OR REJECT A PRODUCT</td>
</tr>
<tr>
<td>PACKAGING</td>
</tr>
<tr>
<td>ARE FINISHED GOODS PACKAGING OPERATIONS SEgregated UNDER SUPERVISED CONTROL</td>
</tr>
<tr>
<td>LABEL RECORDS KEPT</td>
</tr>
<tr>
<td>PART IV - QUALITY CONTROL/ASSURANCE</td>
</tr>
<tr>
<td>DOES THE QUALITY CONTROL/INSPECTION GROUP HAVE FULL AUTHORITY TO HEDULE A BUDGET OR OPERATE INDEPENDENTLY</td>
</tr>
<tr>
<td>TO MANUFACTURE, REWORK, OR REJECT A PRODUCT</td>
</tr>
<tr>
<td>PACKAGING</td>
</tr>
<tr>
<td>ARE FINISHED GOODS PACKAGING OPERATIONS SEgregated UNDER SUPERVISED CONTROL</td>
</tr>
<tr>
<td>LABEL RECORDS KEPT</td>
</tr>
</tbody>
</table>
PART IV -- QUALITY CONTROL/ASSURANCE

ORGANIZATION AND FUNCTION

DOES THE QUALITY
CONTROL-INSPECTION GROUP
REPORT DIRECTLY TO THE TOP,
INDEPENDENT OF PRODUCTION,
MARKETING, OR OTHER
ORGANIZATION GROUPS WITHIN THE
MANUFACTURING COMPANY? (SEE
COMPANY ORGANIZATION CHART)

YEA No

DOES THE QUALITY
CONTROL-INSPECTION GROUP
HAVE FULL AUTHORITY
TO WITHHOLD SHIPMENT OR FURTHER PRODUCTION
OF REJECTED ITEMS

YEA No

ARE THE QUALITY CONTROL PROCEDURES:

IN A FORMAL WRITTEN DOCUMENT

YEA No

REVISED ON A PERIODIC BASIS

YEA No

DOES THE QUALITY CONTROL/ASSURANCE-INSPECTION
GROUP HAVE:

ADEQUATE EDUCATION, TRAINING OR
EXPERIENCE

YEA No

UNDERSTANDING OF THEIR FUNCTION

YEA No OTHER

OPERATIONS

ARE STAMPS, TAGS, MARKERS, ETC.,
USED TO VERIFY INSPECTION ACTIVITY
ARE THE MARKINGS USED TRACEABLE
TO AN INDIVIDUAL INSPECTOR
ARE PRODUCTION SAMPLES FOR QC TESTING:
ADEQUATELY IDENTIFIED AS TO
SOURCES
RECORDED SOMEWHERE AT TIME OF
SAMPLING
ENTERED ON FILED TEST REPORT
WRITTEN SAMPLING PLAN BASED ON:

100% MIL SPEC AQL

RANDOM

IS THE PRODUCT USED TESTED PRIOR
TO FINAL RELEASE

YEA No

ARE OUTSIDE SOURCES USED FOR
PRODUCTION TESTING

YEA No

UNDER FORMAL CONTRACT?

YEA No

USE TEST PROTOCOLS OR WRITTEN PROCEDURES

YEA No

COPIES IN THE MANUFACTURING FILES

YEA No

FACILITY REGISTERED OR LICENSED BY ANY FEDERAL,
STATE OR PROFESSIONAL AGENCY

YEA No

OUTSIDE TEST RESULTS FILED BY THE MANUFACTURER

YEA No

IS THERE A FORMAL QUALITY
ASSURANCE PROGRAM INVOLVING
PERFORMANCE TESTING OF THE
PRODUCT(S) AFTER RELEASE

YEA No

PART V -- CUSTOMER COMPLAINTS AND RECALL CAPABILITIES

CUSTOMER COMPLAINTS

IS THERE AN ORGANIZED COMPLAINT
FILE

YEA No

DOES EACH COMPLAINT STATE:
NATURE OF COMPLAINT
RESPONSE TO CUSTOMER (REPAIR, REFUND, REPLACE)

YEA No

FURTHER CORRECTIVE/PREVENTIVE ACTION BY
MANUFACTURER?

YEA No

COMPLAINT FILES KEPT FOR ______ (YEARS)

YEA No

IS THERE A PERIODIC REVIEW OF
COMPLAINT FILES FOR TRENDS

YEA No

IS THE REVIEW FILE AS A WRITTEN
SUMMARY

YEA No

IS THERE A GROUP OR INDIVIDUAL
ASSIGNED TO HANDLE CUSTOMER
INQUIRIES AND FOLLOW UP ON
COMPLAINTS

YEA No

ARE PRODUCT DEFECTS VERIFIED BY
MANUFACTURER THROUGH TESTING

YEA No

WAS REVIEW OF COMPLAINT FILES FOR
RECALL CAPABILITIES

YEA No

IS THERE A COMPANY RECALL PLAN

YEA No

SHOWS HOW DECISIONS ARE MADE AND BY WHOM

YEA No

HOW RECALL WILL BE ACCOMPLISHED

YEA No

INSTRUCTIONS FOR RECOVERY AND ACCOUNTABILITY OF
RECALLED PRODUCT

YEA No

DO SHIPPING OR DISTRIBUTION RECORDS ON FILE SHOW:

YEA No

CUSTOMER OR DISTRIBUTOR NAME
AND ADDRESS

DATE OF SHIPMENTS AND QUANTITY
SHIPPED

YEA No

LOT OR SERIAL NUMBER OF PRODUCT
SHIPPED

YEA No

DISTRIBUTION RECORDS ARE MAINTAINED
(YEARS)

DISTRIBUTION RECORDS ARE STORED AS:

YEA No

COMPUTER LISTING

MICROFILM/MICROCIRCLE

YEA No

YEA No
**QSR Manual**

**Updated 1/1/1997**

---

**PART VI - REGULATORY COMPLIANCE**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS THE PLANT REGISTERED AS A MANUFACTURER THROUGH TESTING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAS REVIEW OF COMPLAINT FILES FOR SURVEY PRODUCT MADE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS THERE A FILE WITH PAST AND CURRENT LABELING FOR EACH SURVEY PRODUCT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARE THE SURVEY PRODUCT(S) LISTED WITH BUREAU OF MEDICAL DEVICES</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARE ALL NECESSARY APPROVALS FOR MARKETING PRODUCTS AVAILABLE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LIST OF ATTACHMENTS AND COMMENTS**

---

*17-20*
18. Factory Inspections

INTRODUCTION
FDA determines compliance with the GMP requirements set forth in the Quality System (QS) regulation primarily by factory inspections. An FDA inspection of an establishment, however, can be initiated for a number of reasons. The reasons may be general, such as routine scheduling or a need to obtain data on industries new to FDA or, the reasons may be specific, such as investigation of a consumer or trade complaint, a product defect report, an adverse reaction, or a death. FDA also conducts inspections under the Compliance Status Information Systems (Com STAT) on behalf of the Veterans Administration (VA), Department of Defense (DOD), and Health Resources and Services Administration (HRSA). Upon arrival, the investigator presents his/her credentials and issues a Notice of Inspection form FDA 482. At the end of the inspection, observations are recorded on form FDA 483, List of Observations, and discussed with the manufacturer's
management. Later the investigator will write an Establishment Inspection Report (EIR), which is a detailed record of the inspection and findings.

**AUTHORITY AND COVERAGE**

Section 704(a) of the Food, Drug, and Cosmetic (FD&C) Act gives FDA the authority to conduct GMP inspections of medical device manufacturers. During these inspections, facilities, manufacturing processes, records, and corrective action programs are examined by an FDA investigator. The results provide information necessary to evaluate a manufacturer's compliance with the device QS regulation (21 CFR 820).

Anyone who manufactures or stores a medical device can be inspected. A manufacturer is any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributor(s) of devices from foreign entities performing these functions.

**Inspection Plan**

This chapter offers ideas on ways that a manufacturer might prepare for, undergo, and respond to an FDA inspection. First and foremost, it is important to plan ahead! Before being visited by an FDA investigator, a manufacturer should have in place an inspection procedure which takes into account, and prepares a manufacturer for, any eventuality. It should detail company policy regarding an inspection and, very importantly, designate those individual(s) who will work with the FDA investigator. Try to anticipate situations and have written procedures covering them. These procedures will provide continuity from one inspection to another and help assure that corporate policies are followed by employees receiving and accompanying the investigator.

Each person designated as an FDA contact should be chosen carefully and be thoroughly familiar with the inspection procedure and company operations. An inspection will take longer if the contact person cannot answer questions without continually referring to the written procedures. The contact should be familiar with FDA regulations and practices and be able to anticipate problems or requests. FDA contacts should be knowledgeable about plant operations, and able to answer or obtain answers to the investigator's questions. Other individuals, with similar qualifications, should be designated to fill in during absences of the primary contact. A manufacturer might want secondary contacts to accompany the FDA investigator even when the primary contact is present in order for the secondary contact to become familiar with FDA methods and procedures.

Along with the designated contact, the manufacturer may want operations managers to accompany the investigator, such as the production manager, QA manager, etc. These individuals should be familiar with the plant operations and company policy, and be able to answer questions about procedures and processes. However, a manufacturer should keep the number of individuals accompanying the investigator to a minimum to prevent problems such as contradictory statements.

Receptionists should be informed that FDA investigators will eventually visit and have procedures to follow when they arrive. These procedures should include instructions to call the FDA contact person and what to do or who to contact when that person is not available.

**Inspection Refusals**

As noted above, Section 704(a) of the FD&C Act gives FDA authority to conduct inspections. Refusing an inspection may set up an adversarial situation and arouse an investigator's suspicion regarding the manufacturer's compliance with the QS regulation. If a manufacturer refuses an inspection without a valid reason, FDA may obtain a warrant which grants entry for an inspection. Refusals to permit inspection are noted in the manufacturer's file maintained by FDA and may be
interpreted as a lack of cooperation. Moreover, refusal to permit an inspection is a prohibited act under section 301(f) of the FD&C Act, which may result in sanctions that include criminal prosecution and injunction. Moreover, refusal to permit an inspection is a prohibited act under section 301(f) of the FD&C Act, which may result in sanctions that include criminal prosecution and injunction.

There may be instances, however, when a manufacturer needs to ask the investigator to return at a later time to conduct the inspection. Explain why it is best that an inspection be done at a later time. For instance, if the FDA contact person(s) is not in the factory and no one knowledgeable about the manufacturer's operations is available, it may be appropriate to ask the investigator to come back. However, FDA investigators do expect to be admitted if a device factory is operating. The rationale is that if a factory is operating, someone should be in charge and that individual should understand factory operations and procedures. If the factory is not in operation or not yet manufacturing any medical devices, this should be explained to the investigator. The FDA representative may still want to go through the factory to make sure it is not in operation -- manufacturers should have a policy covering this situation. It is advisable, in this situation, to allow the investigator to walk through the factory to verify that it is not in operation. If the factory is not in operation, advise the investigator when operations will begin. The investigator will consider the request and circumstances, then determine whether to proceed with the inspection.

**Inspection Preliminaries**

Before an inspection begins, an investigator is required to show his/her credentials. The credentials have a picture of the investigator and identify him/her as a representative of FDA.

After presenting credentials, the investigator will issue form FDA 482, Notice of Inspection. This form is issued to the owner, operator, or agent in charge of the factory or to the designated FDA contact. The bottom portion of the Notice of Inspection contains excerpts from Section 704 of the FD&C Act. The investigator will complete the top portion of the form by filling in the manufacturer name, address, name of the individual given the signed form, date, and time of inspection. The investigator then signs the form.

The FDA contact person should always be prompt. It is important not to keep the Investigator waiting because misunderstandings can occur regarding the manufacturer's intentions.

**Conduct During the Inspection**

Awareness of what is going on at all times by the contact person of the manufacturer during the inspection is important. Therefore, once started, the inspection should be given priority. If the contact person is distracted by other business, the inspection may be prolonged and the investigator's questions concerning suspected deficiencies may be misunderstood or answered inadequately. Familiarity with the circumstances surrounding any deficiencies listed on form FDA 483 (the list of deviations presented at the close of the inspection) is vital in discussion of these with the investigator.

During inspections, the FDA contact person will deal with many issues such as viewing records, copying, photos of the manufacturing site, tape recordings, differences of opinion, immediate corrections, promises, samples, notes, etc. All of these issues should be addressed by a company procedure.

There should be a procedure for responding to requests for design history records, device master records, quality system records, device history records, change control records, complaint files, and shipping records. All records required by the QS regulation shall be made available to the investigator for review and copying (820.180). Therefore, records required by the QS regulation shall be readily accessible. The procedures covering review of records by the investigator should identify who will retrieve records, how many records can be reviewed at one time and, who should be present to answer questions raised by the investigator.

Because all records required by the QS regulation shall be available for copying, management should decide on a policy...
concerning record copying during inspections. In all situations, the contact should make duplicate copies and keep these
together as a record of the documents that the investigator copied.

If any records copied by an investigator contain confidential information, they should be identified, i.e., by a confidential
stamp. This identification does not automatically prevent release of these records under the Freedom of Information (FOI)
Act; however, the FOI officer filling a request is then made aware that the manufacturer considers the information
confidential. Information deemed confidential by the FOI Act or 21 CFR part 20 shall not be released by the agency.
Reserve "confidential" marking to only those items that are genuinely confidential..

FDA investigators sometimes photograph equipment, conditions, and product at a facility. FDA feels that picture taking is
a normal inspection activity. Include this policy in the inspection procedure.

If the manufacturer disagrees with any observation made by the investigator, be sure to discuss with the investigator the
reason for the observation. You may find that there was a misunderstanding that can easily be corrected. When explaining
situations or answering questions, be honest. Don't make up answers, as this could lead to additional problems. If you don't
know the answer, say so. Personnel with responsibility for representing a manufacturer during an inspection should refer to
the FDA regulations and guidances, whenever possible, rather than base discussions and disagreement on personal opinion.

If there are questions for which you don't have immediate answers, promise to research the questions. A list of these
unanswered questions is a reminder to get the answers and give them to the investigator. The investigator usually records
the questions, and resolving unanswered questions may help avoid inaccuracies on the form FDA 483 and in the
establishment inspection report prepared by the investigator at the end of the inspection.

If possible, any GMP deficiencies that the investigator notes, and on which you agree, should be corrected immediately.
However, before implementing an immediate corrective action, manufacturers should first evaluate their action to assure
that is the best action to take to avoid future quality problems. The investigator should be made aware of these corrections
as this will show intent to comply with the regulations and commitment to quality assurance. Corrective actions that are
verified by FDA during the inspection will be documented in the investigator's EIR.

If correction cannot be made during the inspection, management may want to consider providing an estimated timetable
for correction. However, the manufacturer should not present or commit to a timetable that may be difficult or impossible
to meet. If a timetable cannot be immediately developed, try to get one to FDA as soon as possible.

As with any production change, it is a good idea to discuss possible corrective actions with affected company personnel
before promising correction to FDA. This concept was discussed in Chapter 8, Device Master Record, and Chapter 9,
Document and Change Control, and may prevent promises that have adverse effects on other areas of production. Hastily
conceived corrections can cause greater problems in the long run.

Any commitments made to FDA should have top management concurrence. It can be detrimental to the manufacturer to be
committed to a course of action that cannot be completed or that management refuses to pursue. Therefore, only persons
with the authority to do so should make commitments.

During an inspection, investigators may collect samples. These may be used for a variety of investigational purposes
including:

● to verify conditions in the factory;

● to establish interstate movement of finished devices and their components; or,
CDRH may request samples for a number of reasons, such as surveys of device manufacturers and investigation of user complaints. It is a wise policy for a manufacturer to collect and store duplicate samples whenever an investigator collects samples. If problems are uncovered by FDA, testing of these duplicate samples by the manufacturer may confirm FDA results or form a basis for discussion of FDA findings.

When an FDA investigator collects samples he/she will issue a form FDA 484, Receipt for Samples. Where indicated, interstate movement of the shipments from which these samples were taken will be documented by the investigator with copies of shipping records. The investigator will then prepare an affidavit (forms FDA 463a, 463, 1664a or 1664b) referencing these documents. A responsible employee of the manufacturer will be asked to read the affidavit, identify inaccuracies for correction, and to verify, by signature and/or initials, that the documents referenced in the affidavit pertain to the shipment(s) in question. This action is to formally document interstate receipt or distribution of medical devices. Therefore, the manufacturer should include in its inspection procedure the company policy on the reading and signing of affidavits. Refusal to sign an affidavit is usually noted on the affidavit and in the EIR.

Having accurate and complete knowledge of what an investigator has done is an important part of handling an FDA inspection. Good notes record this information. Comments and suggestions made by the investigator, unanswered questions, and promises should all be recorded. General information on the areas of the plant the investigator visited, to whom he spoke, etc., can help when commenting on form FDA 483 items, making corrections to the facilities or QA system, or advising top management of the results of an inspection.

Notes will also be useful in fulfilling promises or obtaining answers to previously unanswered questions. When the items on the FDA 483 are presented, accurate notes help to prevent surprises. Good notes can also help to prepare well thought out and adequate answers to FDA 483 items even before these items are presented at the close-out meeting.

Close-out Meeting

At the end of an FDA inspection, the investigator conducts a close-out meeting. It is usually held immediately after the inspection, but may take place a day or so later, especially if it takes a long time to prepare form FDA 483. During this meeting, the investigator discusses with company management the observations recorded on the FDA 483 and other observations not listed that the Investigator wishes to bring to management's attention. The manufacturer should compare the form FDA 483 against notes taken during the inspection to confirm the accuracy and completeness of the investigator's recorded observations. Close-out meetings present an opportunity for all parties to correct such misunderstandings. Inaccurate observations will be changed or deleted as appropriate. Top management should be present at the close-out meeting to provide information regarding any planned corrective actions to be taken and schedules for these actions.

The investigator should be reminded of any corrections that have been made. Corrections that have been made during the inspection will be documented in the investigator's establishment inspection report (EIR) if verified by the investigator if time allows, but these observations will still appear on the FDA 483. Mention your plans to make corrections, and provide a timetable for these future actions. Answers given at this meeting will be recorded by the investigator.

After the Inspection

Completion of the inspection by FDA should signal the start of certain activities by the manufacturer, if these activities have not already been initiated, such as discussion of deficiencies with appropriate department employees to advise them
of corrections to be made and time frames involved.

Unresolved form FDA 483 items should be reviewed by company technical and legal personnel. If a decision is made that corrective action is not needed and there is disagreement with the investigator's opinion regarding the deficiency, state this, along with the rationale and documentary evidence, in a letter to the FDA District Office responsible for the inspection. Even if a manufacturer agrees with all the items on the FDA 483, it is a good idea to respond to each item in a letter, along with documentation showing how the corrections have been implemented, to the District Office. The response to the FDA 483 observations should include system corrections and not just "band-aiding" the specific observations. It is very important that the root cause is investigated, where it can be determined, corrected and that appropriate preventive actions take place. This reply shows a commitment to quality assurance and "officially" presents the company's case to FDA. This reply should help resolve any doubts that the inspection report might raise about a manufacturer.

The final step for a manufacturer is to determine what can be learned from the inspection, so that the business can operate in a better state of control, improve quality assurance, and assure future QS compliance.

The following is a concise summary of the major points made in this chapter. This summary should help the manufacturer formulate an inspection plan.

BASIC POINTS FOR AN INSPECTION PLAN

1. Be prepared for the eventual inspection by trying diligently to comply with applicable medical device regulations and preparing an inspection plan. If needed, assistance is available from DSMA, Phone 800-638-2041 and other offices of the Center for Devices and Radiological Health.

Note: DSMA and CDRH can not provide assistance during an FDA inspection by the District office, nor can DSMA provide assistance during an ongoing FDA regulatory action.

2. Receptionists should know who to call when an FDA investigator visits.

3. Determine that an FDA investigator is calling by examining his/her credentials.

4. Receptionists or initial contact persons should inform all key employees that an FDA investigator is present.

5. Someone, but not a large number of individuals, should accompany the investigator and be with the investigator at all times.

6. If the investigator is not familiar with the manufacturer, describe the product line and operations before entering the manufacturing area.

7. At the beginning, review with the investigator all company policies and programs.

8. Employees should be cooperative and seek to avoid conflict. Base discussions on the laws, regulations, guidances, etc.

9. Don't start an argument with, get up-tight with, or lie to the FDA investigator.

10. Understand the investigator's questions before answering. If needed, ask for an explanation. Refer each question to the most suitable employee.

11. Be sensitive to the compliance role of the FDA investigator; do not threaten to call his/her supervisor when the
12. Deviations noted by the investigator should be corrected as soon as possible.

13. Keep duplicate copies or samples of material given to the FDA investigator.

14. During the exit interview, make sure that all deviations are adequately discussed. If there is disagreement, present all of the company information and any regulations and official interpretations that support the company=s viewpoint.

15. Immediately submit to the local FDA District office a written reply to the FDA 483. Make sure you address all of the observations. State how and when you expect to make corrections. If you disagree with an observation, give reasons and references to regulations, guidances, etc., for your position.

16. Be reasonable in setting schedules for corrective actions -- don't state impossible deadlines or drag out completion schedules.

17. A follow-up report covering findings and corrections should be distributed to appropriate company employees.

REGULATORY SANCTIONS

Responsible officials, who are in positions of authority at regulated manufacturing sites, have a primary legal duty to implement whatever measures are necessary to ensure that their products, facilities, and operations are in compliance with the law. The law presumes these individuals are fully aware of their responsibilities.

Whenever FDA determines, as a result of an inspection, investigation, complaint, or other source, that a product is, or may become, adulterated or misbranded, several actions may be taken. These actions may be in the form of a warning letter to the manufacturer; or result in the seizure or detention of a product; or an injunction of the firm and/or responsible individuals; or result in prosecution of the manufacturer and/or responsible individuals. The actions vary depending on the degree of danger to the public or willingness of the manufacturer to correct violations. [Following are several sections of the Food, Drug, and Cosmetic (FD&C) Act commonly used in misbranding or adulteration charges. In this reprint, some key words are bolded for emphasis. Added notes are in brackets.]

**Adulteration**

Section 501 (351). A drug or device shall be deemed to be adulterated --

(a)(1) If it consists in whole or in part of any filthy, putrid, or decomposed substance; or

(2)(A) If it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health;

(c) If it is not subject to the provisions of paragraph 9(b) of this section* and its strength differs from, or its purity or quality falls below, that which it purports or is represented to possess.

[* Paragraph 9(b) refers to drugs].

(h) If it is a device and the methods used in, or the facilities or controls used for its manufacture, packing, storage, or installation are not in conformity with applicable requirements under Section 520(f)(1) or an applicable condition prescribed by an order under Section 520(f)(2).
Misbranding

Section 502 (352). A drug or device shall be deemed to be misbranded --

(a) If its labeling is false or misleading in any particular.

If in a package form unless it bears a label containing (1) the name and place of business of the manufacturer, packer, or distributor; and (2) an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count ...

(f) Unless its labeling bears (1) adequate direction for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods of duration of administration or application, in such manner and form, as are necessary for the protection of users ...

(j) If it is dangerous to health when used in the dosage or manner, or with the frequency or duration prescribed, recommended, or suggested in the labeling thereof.

A device may be considered misbranded for other administrative reasons such as failure of the manufacturer to register, formally list the product, or failure to submit a premarket notification (21 CFR Part 807).

A device may be considered misbranded for other administrative reasons such as failure of the manufacturer to register, formally list the product, or failure to submit a premarket notification (21 CFR Part 807).

When it is consistent with the public interest, it is FDA's policy to: advise regulated manufacturers of potentially violative products, practices, or conditions; advise manufacturers of violations requiring correction; and, give manufacturers an opportunity to make corrections voluntarily before initiating legal or administrative action.

Management Letter

When top management is not present during the issuance of the FDA 483 at the end of the inspection,

FDA may send a Management Letter to top management such as the president, CEO, etc., to assure that top management has a copy of the FDA 483. Because the Management Letter is only a brief transmittal letter, it is not to be considered or confused with the Warning Letter described below.

It is imperative that the manufacturer respond to any recommendations or observations made by the FDA investigator or other official. A written response to the FDA 483, along with documentation to show how the manufacturer has or intends to remove or correct the objectionable conditions or practices, can assure the FDA that the manufacturer has corrected or intends to correct listed violations. The manufacturer should prepare such a response even if they do not hear from FDA in writing. To repeat, a plan of corrective action is very important. Management should evaluate the FDA 483 and their management letter. If they feel any misunderstanding can be resolved by discussion, they may also request a meeting with district management to discuss violations and the manufacturer's proposed courses of action. This approach gives a first hand opportunity to present the case to FDA.

Warning Letter

A Warning Letter is a specifically worded and formatted enforcement letter written by top management of an FDA field or headquarters unit to top management of a manufacturer. The letter is sent by FDA primarily to draw the company's attention to violations and, thereby, obtain prompt correction. A Warning Letter is intended to effect correction of deficiencies noted: during an inspection; from an investigation of a product complaint; or from information received from other sources. A purged Warning Letter is reprinted at the end of this chapter.
A Warning Letter may be issued by FDA instead of immediately seizing product or obtaining an injunction against the manufacturer. The Warning Letter contains a formal warning to the manufacturer advising that specific sections of the law have been violated and, unless corrective action is taken, the FDA is prepared to impose legal and/or administrative sanctions. Sanctions include seizure, prosecution, injunction, and civil penalties. Unless otherwise indicated, within 15 working days after receiving a Warning Letter, a formal response should be made by the manufacturer to FDA. The manufacturer should state the specific steps it has taken to correct noted violations, including an explanation of each step taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

A Warning Letter is also a prior warning and notification to responsible company officials of possible civil or criminal action to be taken by FDA.

Responsible individuals should not assume they will always receive a Warning Letter before FDA initiates administrative action or recommends an injunction, seizure, civil penalty, and/or criminal proceeding. FDA is under no legal obligation to warn manufacturers or individuals that they or their products are in violation of the law, before initiating formal regulatory action.

Remember, the issuance of a Warning Letter to the manufacturer by FDA does not preclude the initiation of other concurrent action, such as seizure, as part of an overall enforcement strategy.

Seizure

A seizure is a civil court action against a specific quantity of goods whereby FDA seeks to remove these goods from commercial channels. After seizure, no one may tamper with the seized goods except by permission of the court. The claimant of the seized merchandise may file a claim and an answer, or may take no action. If no action is taken, the government will move to have the goods forfeited to the government by default. If a claimant decides to contest the Government's charges, the case will be scheduled for trial. A third option allows the owner of the goods to request permission of the court to bring the goods into compliance with the law. The owner of the goods is required to provide a bond (money deposit) to assure that the orders of the Court will be performed and the owner will be ordered to pay for FDA supervision of any activities by the company to bring the goods into compliance.

Detention

An administrative detention prohibits the distribution or use of adulterated or misbranded devices encountered during inspections. The detention usually lasts up to 30 days, and can last longer, until FDA has considered what action it should take concerning the devices, or has initiated legal action if appropriate. During the detention, detained devices may not be used, moved, altered, or tampered with in any manner by any person.

Restraining Orders and Injunctions

A Temporary Restraining Order (TRO) is sought by FDA before an injunction and is designed to stop the alleged violative practice until the court can hear evidence that may lead to an injunction. A TRO imposes restraint upon a defendant for not more than 10 days; this period may be extended by the courts.

An injunction is a court order that restrains a person or manufacturer from violating the law, e.g., to prevent interstate distribution of violative products, and to correct conditions in the establishment in which the violation occurred. FDA may also seek a preliminary injunction. To obtain this preliminary form of relief, the government needs only to show that the law has been violated, and that it will probably continue to be violated unless the court enjoins the violative behavior.
Recalls

The Food and Drug Administration prefers to promote compliance by means other than through the courts. Recall by the manufacturer of violative products from the market is generally the fastest and most effective way to protect the public. A recall may be initiated by the manufacturer or shipper of the product, or initiated by FDA. The first step in a product recall is for the manufacturer or distributor to contact the nearest FDA field office for guidance. FDA can provide technical assistance to small and large manufacturers on how to conduct an effective recall.

It is recommended that manufacturers develop plans which can be put into effect immediately if a recall emergency arises. Accurate and complete product and shipping records are vital to the success of a product recall. Products should be labeled (direct or by code) to show date and place of manufacture.

Recently, FDA has observed that when a manufacturer discovers a risk presented by a medical device, it often voluntarily notifies appropriate persons of this risk in order to reduce or eliminate it. In some cases these notifications meet the definition of recall in 21 CFR Part 7.3(g). There is a proposed rule 21 CFR 810 issued on June 14, 1994, that would establish procedures to implement the medical device recall authority provided in the SMDA. This authority will add to other remedies already available to FDA including rectification, repair, replacement, and refund.

Because of concern that a notification might be classified as a recall, manufacturers have sometimes delayed issuing a notification while discussions are held with FDA. To try to eliminate delays in situations where public health might be at risk, FDA published, "Medical Device Notification and Voluntary Safety Alert Guideline," in March 1984, which contains procedures that manufacturers should use in notifying or alerting health professionals who prescribe or use a medical device. These procedures also describe the steps used by FDA in the notification and safety alert process.

Penalties

FDA has authority to impose civil penalties. Manufacturers are liable for a maximum of $15,000 per violation of the FD&C Act, with a cap of $1,000,000 per proceeding. See Section 303 of the FD&C Act for details of additional penalties. Also, see the Safe Medical Devices Act of 1990 for more details on FDA's authority to impose penalties.

EXHIBITS

Associated with inspections are various FDA forms. Examples of forms are included at the end of this chapter. The form (FDA) numbers are in the lower left corner of each sheet.

Notice of Inspection

The first form is the FDA 482 (Notice of Inspection) which is issued at the beginning of the inspection. It includes blanks for basic information on the manufacturer, the investigator's name, and contains a reprint of applicable sections of the FD&C Act and Public Health Service Act. This form is to be signed by the investigator and given to the individual noted on the form.

Receipt for Samples (page 18-14)

If an investigator collects samples, form FDA 484 (Receipt for Samples) is issued to the company agent. A copy of the receipt needs to be submitted with the firm's invoice or other billing documents if payment has been agreed to by the firm and the FDA Investigator. This form contains the name of the individual given the form, manufacturer information, and sample description. The investigator signs the form and issues it to the individual noted on the form.
Affidavits (pages 18-15 to 18-18)

The next four forms are used where interstate movement of devices is documented by collection of shipping records. The investigator prepares an affidavit (forms FDA 463a, 1664a, or 1664b) referencing these shipping records. A brief statement is included along with space for a description of the documents that relate to the interstate movement of the sample in question. Each form is signed by the investigator and the person giving the information. On one of the sample forms, FDA 463a, the individual giving the information refused to sign the affidavit; and in this case the investigator added a statement to explain the lack of a signature.

List of Observations (page 18-19)

During an inspection, an investigator will note what is considered to be GMP deviations, or deviations from a manufacturer's established procedures. These observations comprise the form FDA 483 (List of Observations) which is issued to the company. The observations are listed in the large blank area of the form, and the form is signed by the investigator. (Page 18-19)

Establishment Inspection Report (pages 18-20 to 18-34)

The final example is the "Establishment Inspection Report". After completion of an inspection, an investigator prepares a comprehensive EIR covering a manufacturer's operations, items on the FDA 483, plus the details that support the FDA 483, and any corrective actions taken by the manufacturer. A manufacturer may receive an unpurged copy of their EIR report under the Freedom of Information (FOI) Act by requesting it in writing from their local FDA District Office. Copies of EIR's requested through FOI by other than the inspected manufacturer will be purged of confidential or trade secret information. The fictitious sample EIR near the end of this chapter has certain lines highlighted to simulate purging. The normally purged material is left in the simulated EIR to show the type of information that would be purged.

Warning Letter (pages 18-35 & 18-36)
Notice of Inspection - A survey given pursuant to Section 704(a) & (b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374) & (d)(2) and/or Part F of G, Title III of the Public Health Service Act (42 U.S.C. 265-264) 2nd Notice of Inspection. The survey was conducted on the premises located at 2704 Sellers St., San Jose, CA. 95131.

Applicable portions of Section 704 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374) are quoted below:

"...if the Secretary finds for good cause that the manufacture, rent, or sale of any such article is dangerous to human life or health..."

Applicable portions of Parts F and G of Title III Public Health Service Act (42 U.S.C. 268-264) are quoted below:

"...if the Secretary finds that the failure..."

Part 4 - "Control of Premises"

Sec. 260a. (a) "If the Secretary finds that the manufacture, rent, or sale of any such article is dangerous to human life or health..."

"...if the Secretary finds that the failure..."
One box of 25-1 cc ampules, Dilaudid ACR (Hydromorphone) 2 mg/cc, lot # 0/03213 manufactured by Knoll Pharmaceuticals Company, Orange, NJ.
STATE OF OREGON
COUNTY OF Klamath

BEFORE ME, SIDNEY H. ROGERS, an employee of the Department of Health and Human Services, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1926, 42 Statutes at Large 303, Reorganization Plan No. IV, Sec. 1215 effective June 30, 1940, Reorganization Plan No. 1 of 1939, Sec. 1-9 effective April 11, 1939 and P.L. 96-80, Sec. 509-92 Statutes at Large 888 (20, U.S.C. 3505), effective May 4, 1990, in administrative tag, affirm, declare, and affirm, personally appearing GEORGE W. HUGHES in the County Court, and State Court within the County of Klamath, the State of Oregon, and the State of Oregon, do the duly sworn, the undersigned says:

I live at 482 Albright Ave, Klamath Falls, Oregon. On October 18, 1980, my neighbor, DR. GEORGE THOMPSON, asked me to pick up some medical instruments from a firm in San Jose, Calif. That same day I drove to San Jose in my 1972 Ford pickup truck which has Oregon license number FAS 682. The next morning, October 19, 1980, I drove to Los Gatos Associates, 920 Arroyo St, San Jose, Calif, and picked up 4 cartons containing a medical device. I drove back to Klamath Falls, Oregon, after picking up a load of fruit, and arrived at about 10 P.M.

The next morning, October 20, 1980, I delivered the 4 cartons to DR. THOMPSON'S office at 2009 Timberline Ave, Klamath Falls, Oregon.

I did not charge DR. THOMPSON to pick up the cartons because I have to make regular trips to San Jose to pick up fruit.

SIGNED AND SWORN TO BEFORE ME, SIDNEY H. ROGERS, on the 2nd day of November, 1980.

SIGNED AT Klamath Falls, Oregon

GEORGE W. HUGHES, OWNER

Hughes Fruit Exchange, 482 Albright Ave, Klamath Falls, OR

Date: 2nd day of November, 1980

State of Oregon

-form thumbnail-
OREGON

KLAMATH

82-876-543

Before me, SONDY H. ROGERS, an employee of the Department of Health and Human Services, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1921, as 33 Statutes at Large, 603 (Reorganization Plan No. V, Sec. 212, effective June 20, 1940; Reorganization Plan No. 1 of 1953, Sec. 1-9, effective July 1, 1953, and P.I. 36-88 Sec. 360a, 33 Statutes at Large 365 (20 U.S.C. 3508)), effective May 4, 1960, to administer or take orders for any drug, article of food, and tobacco, hereby do attest:

GEORGE F. THOMPSON

In the county and state of Oregon, with having duly sworn, deposes and says:

I live at 2209 Timberline Ave, Klamath Falls, Oregon.

In response to an Ad in the August, 1982, "Cascade Sun", I ordered from Los Gatos Associates, 920 Apple St, San Jose, California, 4 Energizer Devices for use in my practice.

On 8-20-82, Mr. George Hughes, Abricio Ave, Klamath Falls, Oregon, delivered to my office the four devices all labeled in part "Isotope Energizer MKX Models Mark I" distributed by Los Gatos Associates, San Jose, California, Serial Numbers 3904, 3905, 2908, and 3907. Mr. Hughes picked up three devices in San Jose for me as he makes regular trips there.

On 9-29-82, U.S. Food and Drug employee, Sidney H. Rogers, took photographs of the devices and copied the label of the four Energizer devices in my office located at 2209 Timberline Ave, Klamath Falls, Oregon.

SIGNED AND SWORN TO BEFORE ME AT __________ CITY AND STATE.

Name: __________________________

City and State:

Date: ____________ Day of __________, 19__.

Employee's Signature:

STATE OF PENNSYLVANIA  
COUNTY OF PHILADELPHIA

Before me, SIDNEY H. ROGERS, an employee of the Department of Health and Human Services, Food and Drug Administration, designated by the Secretary, under authority of the Act of January 31, 1912, 42 Statutes at Large 933, Reorganization Plan No. IV, Sec. 3, effective June 30, 1940, Reorganization Plan No. 1 of 1945, Sec. 1, effective April 13, 1951; and P.L. 90-68, Sec. 209, 93 Statutes at Large 965 (21 U.S.C. 1533), effective May 4, 1980, to administer or take oaths, affirmations, and affidavits, personally appeared PATRICK T. PALMER in the county and State aforesaid, who, being duly sworn, deposes and says: The lot of 325 CASES, 

(24/4½oz cans) OF JOLLY MILLER CANNED MUSHROOMS

which we invoiced and sold to

PATRIOT MARKETS, INC.

FRANKFORD

PENNSYLVANIA

4-12-83

was a portion of a parcel shipped in by

NORTHERN LIGHT FARMS, INC.

DULUTH, MINNESOTA

and is covered by a completed copy of the invoice:

<table>
<thead>
<tr>
<th>NUMBER</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>39/14</td>
<td>4-4-83</td>
</tr>
</tbody>
</table>

and (check all) shipping method:

<table>
<thead>
<tr>
<th>TYPE (ILL,FIB)</th>
<th>NUMBER</th>
<th>DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>B/L</td>
<td>20018</td>
<td>4-5-83</td>
</tr>
</tbody>
</table>

NORTHERN FREIGHT CARRIERS

REMARKS

PATRICK R. PALMER - Wholesale Manager

LIBERTY WHOLESALE GROCERS, 3210 MARY, FRANKFORD, PA 19145

Subscribed and sworn to before me at FRANKFORD, PA.

the 28th day of APRIL 1983

(SIGN AND DATE)

SIDNEY H. ROGERS

(Employee & Signature)

UNITAH

STATE OF

UTAH

May 1, 1982

Because I, Sidney H. Rogers, an employee of the Department of Health and Human Services, Food and Drug Administration, assigned to the Office of the Commissioner, under authority of the Act of January 21, 1932, 43 Statutes at Large 806, Reorganization Plan No. IV, Section 10-11, effective June 30, 1945, Reorganization Plan No. 5 of 1935, sect. 2, effective April 11, 1953, and P.L. 77-237, as 778, 43 Statutes at Large, 26 U.S.C. 251(b), effective July 1, 1969, am authorized for the taking, collection, inspection, and analysis, personally appointed,

WAYNE J. ELLMORE

in the county and State above, who, having duly sworn, do and do affirm

I am employed by

TRANS-NATIONAL TRUCK LINES, TULSA, OKLAHOMA

named for name of firm

as DRIVER

Title of position

On October 14, 1982, at VERNAL, UTAH

Date

the above named FDA employee collected a sample consisting of

TWO CRATES (48 HEADS PER CRATE)

of POLAR BRAND, ICEBERG LETTUCE, PACKED BY DEBORT BROTHERS LETTUCE SUPPLIERS, FRESNO, CAL.

TRACTOR TRAILER #231, OKLAHOMA LIC. #8-07379, 1982.

Tractor type and number & Tractor number or name of truck, may, if any, explained, used for identification and shipping

From intermediate to additional disclosure of:

MID CENTRAL DISTRIBUTORS, 33 FRONT ST, MINNEAPOLIS

MINNESOTA

Consignee name & address:

The above described shipment contained by WAYNE J.

ELLMORE

Truck Driver

(name of individual

making identification

(type of personal identification number;

Number & Shipping Record A-32196

(date of entry into national interstate commerce

issued by TRANS-NATIONAL

TRUCK LINES

which were identified by WAYNE J. ELLMORE,

 Neue 25/01/1982

(date & name of individual

issuing identification

confirming records

WAYNE J. ELLMORE

Affidavit's signature

file:///C|/Users/HP_Administrator/AppData/Local/Temp/msohtml1.00/content0/0.png
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**

<table>
<thead>
<tr>
<th>DISTRICT ADDRESS AND PHONE NUMBER</th>
<th>NAME OF INDIVIDUAL TO WHOM REPORT ISSUED</th>
<th>DATE OF INSPECTION</th>
<th>F. I. P. NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minneapolis District</td>
<td>William S. Gundstrom</td>
<td>Jan. 5 thru 7, 1982</td>
<td></td>
</tr>
<tr>
<td>240 Hennepin Ave.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minneapolis, MN 55401</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(612) 722-2121</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIRM NAME**  
Tepline Pharmaceuticals "T.L.P.",

**STREET ADDRESS**  
2136 Elbe Place,

**CITY AND STATE**  
Jackson, MN 55326

<table>
<thead>
<tr>
<th>NAME OF FIRM, BRANCH OR UNIT INSPECTED</th>
<th>STREET ADDRESS OF FIRM, BRANCH OR UNIT INSPECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;T.L.P.&quot; Division 03</td>
<td>80 Elbe Court</td>
</tr>
</tbody>
</table>

**DURING AN INSPECTION OF YOUR FIRM:**  
(See IQM 512, 512.1, & 512.2)

List your observations in a logical and concise manner.

(See IQM 512, 512.1, & 512.2)
ESTABLISHMENT REPORT (EIR) PURGED

SUMMARY OF FINDINGS

This inspection was conducted in accordance with the NYK-DO June 1986 Workplan, under CP 7378.830 Inspection of Medical Device Manufacturers, and under CP 7378.830A Sterilization of Medical Devices. This inspection was also conducted to follow up medical device complaint M-00210, dated 5/31/84, re: leaking of a Cardio-Minipor IV Filter (no specific lot number).

This firm produces various sterile disposable blood filters and cardiovascular catheters. This inspection was limited to the firm's sterile blood filter which is intended for extracorporeal use as indicated during any cardiopulmonary bypass procedure (open heart surgery). This product is currently classified as a noncritical device.

Previous inspection 6/82 was performed as a follow up to PHI-DO memo 4/2/82 (J.L. Smith) requesting information on validation studies, and the firm's controls for testing for sterility and ETO residues. PHI-DO=s inspection of a contract sterilizer, Minix Lab, Erie, PA, revealed the firm had no validation study and that the firm failed to follow its own established ETO process parameters. NYK-DO=s 6/82 inspection revealed that sterility testing and controls were adequate, that an ETO residue study had been conducted and that the firm was conducting a validation study. No FD 483 was issued, and no samples were collected.

Next previous inspection, 12/20/81, was conducted as a follow up of two medical device problem reports, M32012 and M32190, both concerning leakage during use of the firm's IV filter. Inspection revealed that the product probably failed due to its being used as pressures in excess of 600 mm Hg, as filters from the same lot passed this specification upon retesting. No FD 483 was issued.

The current inspection revealed some deficiencies in the firm's master device record for the blood filters. No other deficiencies were noted. The deficiencies were listed on an FD 483, which was presented to and discussed with management at the close of the inspection. Deficiencies noted in the master device record are:
1. it does not list acceptance criteria for incoming components;

2. it does not list that components made of plastic are to receive an IR spectrographic analysis;

3. it does not list that the cellulose acetate filtering material is about 120 mesh, nor does it list the quantity of this material that is used to manufacturer blood filters;

4. the operation sheets have not been signed by all approving officials;

5. the engineering diagrams for the housing, and top end cap do not bear the signature/initials of an approving corporate official.

Management promised correction of the noted deficiencies, and stated that they had already attended to the first point (Ex. 8). No samples were collected during this inspection.

Investigation of complaint M-00210 revealed that the IV filter had probably been subjected to pressures in excess of 600 mm mercury. The product is labeled for use below 600 mm mercury.

Current inspection also revealed that the firm intends to discontinue using Minix Lab as the contract sterilizer. The firm intends to develop/perform its own ETO sterilization procedures within the next year.

On 6/7 to 9/84, I was accompanied by John Goodguy. Mr. Goodguy represents the Center for Devices and Radiological Health, Division of Small Manufacturers Assistance. Mr. Goodguy wanted to become familiar with the way FDA field offices were conducting medical device inspections. Mr. Goodguy=s tight schedule did not permit him to accompany me for the complete inspection.

HISTORY OF BUSINESS

The firm is a New York State corporation with the following corporate officers:

Mrs. Alice B. Potts Chairman of the Board
Mr. John (NMI) Fogg President
Mr. William L. Pearl Senior Vice President
Mr. Walter Y. Ratkowski Vice President and General Manager

Cardio-Medical Products, Inc. is a wholly owned subsidiary of Medical Products USA, Inc. and both firms occupy the same premises. The corporate officers of Medical Products USA, Inc. are:

Dr. Michael P. Heart Chairman of the Board
Mrs. Alice B. Potts President
Dr. Mary L. Day Executive Vice President
Mr. John (NMI) Fogg Senior Vice President

Filters are manufacturers under the Cardio Minipor trade name and in general are intended for hospital use. The firm manufacturers four types of filters, as follows:

1. Blood Dialysis Filters
2. Cardiopulmonary Bypass Blood Filters

3. Infusion Line Filter

4. IV Filter

The firm operates 3 shifts (24 hours per day) Mon.-Fri., except for two weeks around Christmas. The firm also closes for two weeks in July for major cleaning operations. The firm is currently registered as a medical device establishment.

PERSONS INTERVIEWED AND INDIVIDUAL RESPONSIBILITY

At the start of the inspection credentials were shown and an FD 482, Notice of Inspection, was issued to Mr. John (NMI) Fogg, President. Credentials were also shown to Dr. Paul M. Turner, Ph.D., Quality Assurance manager, and to Mr. Thomas (NMI) Romano, Quality Control Manager.

During this inspection, I was also introduced to: William L. Pearl, Senior Vice President; Walter Y. Ratkowski, Vice President and General Manager; Charles Miller, Asst. QC Manager; Alice Oprice, QA Technical Assistance; Joseph DiRisio, Metrologist; Harold Miller, Operations Manager; and Katherine Anderson, Materials Manager. Mr. Fogg and/or Dr. Turner accompanied me during most of the inspection and supplied most of the relevant information. Some relevant information was also supplied by the above named individuals.

At the close of the inspection and FD 483, Inspectional Observations, was issued to and discussed with Mr. John (NMI) Fogg, President.

Key officers/plant personnel are as follows:

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>John (NMI) Fogg</td>
<td>President</td>
</tr>
<tr>
<td>William L. Pearl</td>
<td>Senior Vice President</td>
</tr>
<tr>
<td>Walter Y. Ratkowski</td>
<td>Vice President and General Manager</td>
</tr>
<tr>
<td>Dr. Paul M. Turner</td>
<td>Quality Assurance Manager</td>
</tr>
<tr>
<td>Thomas (NMI) Romano</td>
<td>Quality Control Manager</td>
</tr>
<tr>
<td>Charles Miller</td>
<td>Asst. Quality Control Manager</td>
</tr>
<tr>
<td>Harold Miller (brother)</td>
<td>Operations Manager</td>
</tr>
<tr>
<td>Joseph DiRisio</td>
<td>Metrologist</td>
</tr>
<tr>
<td>John Dace</td>
<td>Vice President</td>
</tr>
</tbody>
</table>

Mr. John Fogg stated he was the firm's president and chief executive officer, and bore overall responsibility and authority for the firm's activities (see Ex. 1, pg. 4). Mr. Fogg stated that he could authorize capital expenditures on his own authority, and that he did not have to obtain authorization from any official of the parent firm before making a capital expenditure. Mr. Fogg stated he was responsible for authorizing research and development programs, marketing programs, allocation of space, new construction, plant maintenance, acquisition of capital equipment, labeling changes, and for authorizing any studies such as validation studies, bioburden studies, and residue studies.

Mr. Fogg stated that William L. Pearl, Sr. VP, was responsible for him for engineering; that Dr. Paul M. Turner, QA Manager, was responsible for him for the QA program; that Thomas Romano, QC Manager, was responsible for him for the routine review and approval of device history records and for the release of lots from quarantine; that Harold Miller,
Operations Manager, was responsible to him for production and warehouse activities; and that Walter Ratkowski, VP and General Manager, was responsible to him for sales and marketing operations. Mr. Fogg stated he has a BS in Chemistry from Furman University, Greenwich, South Carolina, has been with the firm since 1962, and has been president for about the last eight years.

During the inspection Mr. Fogg directed various employees, such as Dr. Turner, Mr. Romano, Mr. Harold Miller, and Ms. Oprice to provide me with requested information. These requests for information were honored by the various employees.

William L. Pearl, Sr. VP, stated he was responsible to John Fogg for engineering. These responsibilities include reviewing and approving engineering diagrams, research and development projects for new equipment and new products, and performing major equipment overhauls. Mr. Pearl has been with the firm since 1969 and has a BS in Mechanical Engineering from Duke University, Durham, North Carolina.

Walter Y. Ratkowski, VP and General manager, is responsible for sales and marketing operations to John Fogg. As a follow up to a product occurrence report (complain) Mr. Ratkowski is responsible for determining if and when complimentary replacement units are to be sent out. Mr. Ratkowski has a BS in Chemical Engineering from the University of Toronto and has been with the firm since 1968.

Paul M. Turner, QA manager, stated he was responsible to John Fogg for the quality assurance program of Cardio-Medical Products, Inc. These responsibilities include the periodic auditing of production, lab quality control, and metrology procedures, implementing studies authorized by Mr. Fogg, and ensuring that the firm meets its regulatory responsibilities and complies with GMP regulations. Dr. Turner stated that it was his responsibility to prepare and submit 510(k)s to the FDA. Dr. Turner has his Ph.D. in Chemistry from Western Michigan University, Kalamazoo, Michigan and has been with the firm since 1976.

Thomas Romano, QC Manager, stated he is responsible to Mr. Fogg for renewing and approving device history records to determine if a lot of finished filters can be released from quarantine and entered into inventory, for the inspection and approval of incoming components, for the activities and records of the QC labs in performing tests on incoming components, in process products, environmental plates, bioburden, and pyrogen.

Mr. Romano stated he coordinates complaint investigations by reviewing complaints and deciding which department(s) will be responsible for investigating the complaint, and is responsible for sending out responses to complaints when necessary. Mr. Romano stated that Mr. Charles Miller, Asst. QC Manager, assists him in his duties. Mr. Miller is also responsible for maintaining the firm's reserve samples, which are used for stability study purposes only. Mr. Romano has his BS in Chemistry from Wright State, Dayton, Ohio and has been with the firm since 1978. Mr. Charles Miller has his BS in Biology from Yale University, New Haven, Connecticut and has been with the firm since 1977.

Joseph DiRisio, QA Metrologist, stated he was responsible to Dr. Turner for all of the firm's metrology (measurement and calibration) functions, and that he originated the firm's metrology manual (Ex. 4). Mr. DiRisio stated he was formerly the metrologist for American Armature Co., Cleveland Ohio and that he has been with the firm since 1976.

Harold Miller, Operations Manager, stated he was responsible to John Fogg for production and warehouse operations. Mr. Miller is also responsible for ordering raw materials and for routine maintenance and clean up operations. Mr. Miller has his BS in Mathematics from New York University and has his MS in Industrial Engineering from Columbia University, New York, New York and has been with the firm since 1979.

GUARANTEES AND LABELING AGREEMENTS
The firm does not offer and FD&C guarantees. Dr. Turner stated that the firm does have agreements with some of their component suppliers whereby suppliers have agreed to notify Cardio-Medical of any changes in components, testing or procedures related to the manufacture of the components. Dr. Turner provided me with copies of these agreements (Ex. 10). These agreements appear to satisfy the GMP regulation re: critical component supplier agreements, although the firm is not required to have these agreements as the device is currently classified as a non-critical device. The firm also ships some filters in bulk to overseas divisions/subsidiaries of Cardio-Medical Products, Inc. without the need of a labeling agreement.

FIRM'S TRAINING PROGRAM

The firm's training program for production employees consists of on-the-job training and lectures. Mr. Fogg stated that any formal training given to employees is documented and recorded in the employee=s personnel file. I requested Mr. Fogg to remove the documentation of Mr. Joseph DiRisio=s training from his personnel file for my review. Training was adequately documented.

RAW MATERIALS

Raw materials and components used to manufacture the firm's blood filters include:

<table>
<thead>
<tr>
<th>Materials</th>
<th>Suppliers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gellulose Acetate</td>
<td>Macomb Laboratories, inc. (Bohemia, NY)</td>
</tr>
<tr>
<td>Bonding epoxy</td>
<td>Ideal Materials Co. (Toledo, Ohio)</td>
</tr>
<tr>
<td>Polyprepylene end cape</td>
<td>ABO Excruders Inc. (Los Angeles, CA)</td>
</tr>
<tr>
<td>Glycerine Lubricant</td>
<td>Sigma Laboratories (Miami, Florida)</td>
</tr>
<tr>
<td>Ultrasonic cleaning solution</td>
<td>Ace Science Inc. (Kenilworth, NJ)</td>
</tr>
<tr>
<td>Polypropylene tubing</td>
<td>ABO Excruders Inc. (Los Angeles, CA)</td>
</tr>
</tbody>
</table>

Components used to manufacture the firm's filters are listed in Ex. 6 Suppliers' addresses are listed in Ex. 7.

Components are stored in the firm's warehouse, located down the block at 2700 Ogden Street. Incoming components are stored in a chaged quarantine area in the warehouse. When components are inspected and found to be acceptable, cartons containing the components are each ink stamped AACCEPTED.@ The firm does not use the system of designating quarantined components with a AQUARANTINE@ stamp of sticker, and then subsequently identifying the component as AACCEPTED@ or AREJECTED.@

Mr. Fogg stated that Quality Control inspectors inspect incoming components for characteristics as specified in the master device record. Ex. 8 is an example of the characteristics for some of the blood filter components listed in the master record. Though QC inspects components for these characteristics, no pass-fail specifications were noted during the inspection. This was pointed out to Mr. Fogg and Dr. Turner. By the conclusion of the inspection, Mr. Romano had drafted up such a specification, as is shown on Page 1 of Ex. 8.

All incoming components are assigned a control number, which reflects the purchase order number (P.O.#). For example, if P.O.#23466 is for 200 cartons of filtermesh and the order is received from the supplier in several shipments, then the cartons in the first shipment will be identified with control number 23466-1, and the cartons in the second shipment will be identified 23466-2, and so on until all the cartons shipped under this purchase order are received. This information is recorded manually as well as fed into the firm's computer. The computer is used for inventory control and facilitates the firm's first-in, first-out policy.
Mr. Romano described the components inspection procedure. Components are inspected for the characteristics specified in the device master record (see Ex. 8) which requires that 10% of the log, up to 1,000 units, be inspected. A QC inspector can accept the lot if he finds no defective units; otherwise a deficient lot will have to be approved by the firm's Materials Review Board (William Pearl, John Fogg, and Thomas Romano).

During the inspection a QC Inspector was noted to be inspecting an incoming lot of housing units for the blood filter. Upon questioning, the inspector stated that he checks the housing units using a B&L 200X stereoscopic microscope and standardized micrometer. The inspector stated he checked each sampled unit for burro and sharp edges using the microscope. The micrometer was used to check the wall thickness of the housing. The tolerance spec for the wall thickness was 0.01 cm.

Using one of several microscopes, the firm's QC lab checks the cellulose acetate filtering material for mesh count of every lot of mesh received, and records the results of the inspection in a log book. This log book cross-references the purchase order number of the lot.

OPERATIONS

The firm occupies a two story building in a light industrial area: the first floor is mainly for plant operations and the second floor is mainly for office space. As previously stated, the premises are shared between Cardio-Medical Products, Inc. and Medical Products USA. Cardio-Medical Products has 65 employees, working three shifts Mon.-Fri. The firm is closed for two weeks around Christmas and In July. The firm has a warehouse at 2700 Ogden Street which is used to store raw materials and finished products. Finished products ready for ETO sterilization are shipped to the contract sterilizer via company trucks. Finished products ready for distribution to consignees are usually shipped via UPS.

Mr. Fogg estimated that his firm manufactured about 10,000 blood filters last year, of which about 3,000 were used for arterial use, and about 7,000 were used for cardionomy use. Blood filters are manufactured to be compatible with either 2 inch or 1 inch connectors. The bulk of the firm's blood filters are manufactured with 2 inch connectors.

The manufacturing operations are listed and described in the master device record=s AOPERATION SHEETS.@ Ex. 11 is an example of some of the AOPERATION SHEETS.@ In essence, the manufacturing process consists of the following operations:

1. Molding of plastic parts. Appropriate quantities of virgin resin (60%) and regrind resin (20%) are selected and weighed. Red #12 is added and the material is mixed.

2. The above mixture is dated and given a lot number and placed into a sized tumbling device (Rich Hopper) for blending for 6 hours.

3. Prior to using the molding, machine is purged of any previous materials. A mixture of mold release agents is used. This is forced thru the system using air at 50 PSI.

4. After flushing with mold release agents, the system is lubricated using a glycerin lubricant manufactured by Sigma Labs, Miami, Florida.

5. The molding machine is set up using the appropriate mold. The firm has 4 different molds. Two molds are used for the arterial filter, one for 1 inch connectors and one for 2 inch connectors. The other 2 are for cardionomy filters, again 1 for 1 inch and the other for 2 for 2 inch connectors.
6. When the plastic parts have been molded, the cellulose acetate filtering material must be inserted. This is done by a special machine which places one layer of material on top of another. The completed filter has a total of 60 layers for the arterial model and 75 for the cardionomy model.

7. After the cellulose acetate has been inserted into the filter, the end cap is placed on the open end and bonded using a bonding epoxy. This operation is performed using a specially designed capping machine. Epoxy is applied to the cap at one state of the machine operation, then the cap is inserted into the body of the filter. The machine then twists the cap into place.

8. Once the cap and body have been applied, the polyurethane tubing is attached to either end of the filter. The tubing is received in a large spool and cut to the proper length using a Ronfro tube cutter model 54.

9. The finished filter is then placed into its metal housing and then into polypropylene bags which are sealed using a Smith #2 heat sealing machine. The bags are then loaded into cartons, 10 filters to a carton for shipment to the contract sterilizer. Each carton is labeled as Acaution, this product has not yet undergone sterilization@.

10. When the sterilized product is returned, samples are removed and the cartons placed in a quarantine area. When the results of the sterility test are received, the cartons are marked Aapproved for packaging.@ The final step in the process is the packaging of the filters into labeled cardboard unit packages. This is accomplished using a Packo packaging machine model #8245. Once packaged, the product is stored in a quarantined area until released for shipping.

Samples designated for testing are pulled by QC. The firm performs its own Bubble Point SSP/NF testing of each lot of filters prior to ETO sterilization. See Ex. 16 for USP/NF Bubble Point testing procedures and Ex. 17, pages 20-22, for some Bubble Point log book records. See Ex. 14 for bioburden testing procedures and Ex. 17, pages 23 and 24, for LAL Pyrogen Testing log book records.

Filters designated for sterility testing are held separate from the rest of the lot until the lot is ready for shipment to the contract sterilizer. Samples designated for pyrogen and safety (toxicity) testing, by outside labs, are also pulled at this time.

The firm's QC lab was noted to have on hand the Jones Bubble Point Testing Apparatus to test the filters prior to ETO sterilization. These were calibrated at 0.001 ml. of air per cubic inch.

The firm also performs its own LAL pyrogen testing. This pyrogen testing is performed on the IV filter only, as only these filters have a Lewis Crenshaw filtering media. All other filters have Wren media, which are not as likely to support bacterial growth as Lewis Crenshaw media. The firm's QC lab had Pyro Gen Lab test serum and testing apparatus. Review of LAL testing records going back 6 months revealed no positive results. Charles Miller, Asst. QC Manager, stated that QC lab uses a 40% alcohol solution as first a rinse on the filter, a 25% solution as a second rinse to collect the solution used for pyrogen testing and a 10 unit sample for each testing run.

The rest of the cartons in the lot are pelletized and the pallets are completely wrapped with large sheets of cardboard and banded with steel bands to discourage tampering. Each pallet is identified with a Cardio-Medical sterilization lot number, which is a number that can be correlated to the contract sterilizer's sterilization lot number. Each pallet is also identified with a contents statement, indicating the product numbers, day lot numbers, and the number of cartons of each lot contained on the pallet. A Cardio-Medical truck will take up to 6 pallets of products to the contract sterilizer, Minix Lab, Brie, PA about once a week. The filters designated for testing by outside labs are shipped along with the pallets to the contract sterilizer. Through contractual agreements Cardio-Medical has notified the contract sterilizer of the desired placement of the test samples within the sterilizer, as shown in Ex. 20, Pg. 3. For each sterilization lot Cardio-Medical notifies the contract sterilizer which samples are not to be sent to which outside labs. A Cardio-Medical truck will pick up

file:///C|/Documents%20and%20Settings/HP_Administrato...sktop/Linked%20Files/Design_Controls/QSR/18inspn.html (25 of 34)6/13/2005 7:49:01 PM
he lot after it has been sterilized, and return it to the Cardio-Medical warehouse at 2700 Ogden Street, where the lot is placed in quarantine until the test results are returned and approved.

In the meantime, QC personnel will open up 6 cartons from each day lot of all the day lots in each sterilization lot and inspect the plastic bags for any air leaks/burst bags. If any air leaks/burst bags are found, then every carton in the day lot is opened to determine how extensive the problem is. Leaks/burst bags indicate either the bags were not sealed properly and/or that the contract sterilizer pulled a vacuum larger than they should have during the ETO sterilization cycle. Lots found with the significant numbers of leaks/burst bags are re-bagged and subjected again to ETO.

Once the QC Manager approves of the QC inspection tests and approves of the outside testing lab results (sterility, pyrogen, and safety), then he will sign the lot release report (Ex. 17, Pg. 1) which permits the release of the lot from quarantine and entry into inventory.

Mr. Charles Miller stated that he maintains the firm's reserve samples which are collected 10 times a year and are used for shelf life studies (see Ex. 22). No other reserve samples are taken. Shelf life studies testing includes tests for Bubble Point, Porosity and Sterility.

Regarding components and products rejected during processing, Mr. Fogg stated that all rejects are discarded, rather than shipped back to the supplier. Mr. Fogg stated that his firm preferred to use only components made from polypropylene, and that to avoid any of the problems associated with recycling, his firm did not ship rejected components (rejected during processing) back to the suppliers. Rejects are taken to the Smith & Company incinerator about 5 times a year for destruction. Mr. Fogg stated that his firm documented these destructions, and showed me the records covering the most recent destruction.

METROLOGY

Mr. Joseph DiRisio, QA Metrologist, stated he was responsible to Dr. Paul Turner for all the firm's metrology (measurement and calibration) operations. Mr. DiRisio stated he maintains the logs and records that show when equipment was last serviced, who serviced it, what the calibration errors are, if any, and when the next service calibration is scheduled. Each piece of production and testing equipment is assigned a unique number for calibration record purposes. As can be seen in Ex. 4, the firm has primary standards, for which calibration is recorded traceable to the National Bureau of Standards (NBS). Primary standards consist of transfer equipment such as weight sets, lengths, thermocouples and digital multi meters. These standards are calibrated by Calibra Metrologist, Inc. White Plains, New York. Mr. DiRisio showed me the metrology manual and some of the records covering the servicing and calibration of equipment. Inspection revealed that the firm's laminar-flow hoods were serviced by Lami Flow, Ltd. New York, New York and that the firm has records to show that the hoods were serviced about every 6 months going back to 12/76. The most recent service was in 2/84.

POROSITY STUDIES

The firm has an ongoing porosity study program. Products from each day's production are tested for porosity by the firm's QC lab. Ex. 17, pages 23 and 24, are examples of the records for routine porosity testing. Mr. Fogg and Dr. Turner stated that routine porosity testing was a good QA procedure to establish a long term history of their products, and was much more valid than a one shot porosity study.

VALIDATION OF STERILIZATION

ETO sterilization has always been performed by an outside contracted firm, Minix Labs, Erie, PA. Mr. Fogg stated that Minix has never disclosed its ETO sterilization cycle parameters, feeling that such information was proprietary and that
such information would not be released unless Cardio-Medical agreed not to make use of this information for its own purposes and agreed to release this information to any firm that might make use of this trade secret information. Mr. Fogg stated that Cardio-Medical was not able to agree to such a proposal. As such, Cardio-Medical asked Minix Labs, Erie, PA to conduct a validation study using Cardio-Medical's parameters, on Cardio-Medical's newest product, the IV fluid filter/air eliminator. This study is attached as Ex. 20, and was conducted in 1978. Mr. Fogg stated that this study determined that ten to the minus 6 kill could be achieved in 14 hours using their parameters, and that, as a safety feature Minix Labs has been asked to sterilize Cardio-Medical's filters to the equivalence of 16 hours of Cardio-Medical's ETO sterilization parameters.

The sterilization validation study (Ex. 20) lists the parameters of the sterilization cycle (Pg. 1), the configuration of the test samples (Pg. 3), the protocol of the study (Pg. 1), the records and results of the study (Pages 8-34) and other information.

Mr. Fogg stated that his firm intended to discontinue using this contract sterilizer, and start using a sterilization procedure of their own, in about 6 months. Mr. Fogg stated that the proposed sterilization procedures would involve placing cartons of filters into each 3x2x1 foot aluminum orib. The orib would then be filled with 80% ETO, 20% mix. After 10 hours of exposure, the cartons would be removed from the orib and routed to the holding room for 24 hours. Mr. Fogg stated that his firm has been consulting with Steri Consultant, Inc and would be consulting with FDA's Dr. Bruch re this proposed ETO sterilization procedure, and methods to validate this procedure.

DEVICE HISTORY RECORDS

Device history records are maintained by sequential Cardio-Medical sterilization lot numbers. During this inspection, the most recently completed device history record available for review was for sterilization lot #340, for which the lot release report was signed on 5/29/84. Sterilization lot #340 contains the records for 26 lots (aday lots@) of blood filters (see Pg. 17 of Ex. 17). Day lot #00441 was randomly picked as the device who=s record I would review. Ex. 17 consists of most of the device history records relevant to sterilization lot #340, day lot #00441, which consists of records as follows:

PAGE SUBJECT

1 Lot release report
2-4 Component Materials Record - lists the lot numbers of the components used in day lot #00441
5-13 Operation Cards - shows the who, what, when, and how many of each manufacturing step; and that the lot was divided into 9 tote boxes for easy handling
14-15 Forms Traceability
16 Inspection of Vacuum Bag Integrity
17 Material Movement Report - shows which pallet day lot #00441 was placed on, out of 4 pallets
18-19 In Process Testing Report - shows that day lot #00441 was subject to porosity testing and USP/NF Bubble testing as well as LAL Pyrogen testing. The firm's LAL pyrogen testing procedure is described in Ex. 16.
20-22 QC Lab Book - shows the results of Bubble Point testing
23-24 QC Lab Book - shows the results of LAL testing
25 Transfer Receiving Report - lists the products and quantities shipped to the contract sterilizer

26 QC Lab Book - shows the day lots of quantities which were designated for sterility testing by Steri Consult, Inc., Boston, MA and the day lots which were designated for pyrogen and safety testing by Test All Ltd., Patterson, NJ

27 Letter, dated 5/1/84, directing Steri Consult, Inc. to test for pyrogens and safety

28 Letter, dated 5/1/84, directing Steri Consult, Inc. to test filters for sterility

29 Letter, dated 5/9/84, re: results of pyrogen testing

30 Letter, dated 5/12/84, re: results of safety and testing

31-32 Letter, dated 5/6/84, re: results of sterility testing

33 Final Inspection Record - inspection of lot after sterilization

DEVICE MASTER RECORD

During this inspection the firm's device master record for their Minipor Blood Filter was reviewed. Review of this record revealed that it contained, or referred to, almost all of the information required by the device GMPs (device specifications, manufacturing processes, quality assurance procedures, and packaging and labeling information). Only some minor deficiencies were noted. These are discussed under Objectionable Conditions. Information relevant to the device master record is contained in Exhibits 6 thru 16.

OBJECTIONABLE CONDITIONS

During this inspection the only objectionable conditions noted were some minor deficiencies in the device master record for the Minipor Blood Filters. These deficiencies were listed on an FD 483, Inspectional Observations, which was presented to and discussed with management at the close of the inspection.

Deficiencies noted were:

1. it does not list acceptance criteria for incoming components;

2. it does not list that components made of plastic are to receive an I.R. spectrographic analysis;

3. it does not list that the cellulose acetate filtering material is about 120 mesh, and it does not list the quantity of this material used to manufacture the blood filters;

4. the Operation Sheets have not been signed by all approving officials (Ex. II); and

5. the engineering diagrams for the housing, and top end caps do not bear the signature or initials of an approving corporate official (Ex. 12).

No other objectionable conditions were noted during this inspections.
MANUFACTURING CODES

The firm uses two manufacturing codes: a day lot code and a sterilization date code. The day lot code is a code that represents the date the product was manufactured (assembled). For example: A00441" means the 4th day of 1984, the 1st shift, where 004 if the fourth day, 4 is 1984, and 1 is the first shift. The sterilization date code AJan 30 1984" is self explanatory.

The day lot code is ink stamped on every box and every carton, prior to EtO sterilization. The sterilization date code is ink stamped on every carton after the lot returns form Ethylene Oxide sterilization. The firm does not have a policy of coding the actual filter nor of coding the stick-on label applied to the filters.

CONSUMER COMPLAINTS

During this inspection the firm's consumer complaint file was reviewed, and a follow up was made of Medical Device Complaint M-00210 dated 5/31/84, which concerned leaking of Cardio Minipor IV Filter (no lot number given). Mr. Fogg stated that his firm had investigated this complaint and had determined that the hospital did not normally use their filters, and that the nurse that had registered the complaint was not familiar with its use. A company representative visited the hospital and talked with the nurse about the application of the IV filter.

Mr. Fogg stated that the filter was designed for use at pressures under 600 mm of mercury, and that at above 600 mm of mercury the filter would crack in such a way as to maintain the integrity of solutions on the downstream side of the filter, and also prevent any air bubbles form getting into the system. M-00210 is attached as Exhibit 23, pages 5-8. The labeling for the IV filter specifically states that the filter is not to be used at above 600 mm pressure of mercury.

Review of the firm's complaint file revealed 10 complaints registered since 12/78 (excluding the above complaint), which the firm has assigned as number 91, 93, 94, 96, 97, 98, 100, 101, 102, and 103. Three complaints concerned Minipor blood filters, four complaints concerned blood dialysis filters, and three complaints concerned cardiovascular catheters concerning packaging defects, embedded particulate matter, cracks and leaks.

Mr. Fogg stated that all complaints are evaluated and investigated. Mr. Thomas Romano stated he evaluates all complaints to determine which department(s) should investigate the complaint. If available, sample of the subject lot are re-tested to determine if the complaint can be duplicated. Complaints are evaluated to determine if the complaint can be duplicated. Complaints are evaluated to determine if changes in QC or production procedures are needed, and to see if there are any patterns. Dr. Turner stated that during routine production, lots are subject to 100% checks and to a statistical check, in an effort to prevent any defects from leaving the plant. Mr. Romano stated that copies of complaints and the investigations are routinely routed to John Fogg, Dr. Paul Turner, and to William Pearl.

PROMOTION & DISTRIBUTION

Mr. Fogg stated that the firm distributes its filters nationwide, and overseas to Italy and Germany. Filters are sold to distributors who, in turn, sell the filters to hospitals. The firm's service representatives, both here and abroad, give lectures on the applications and proper use of Cardio-Medical=s filters. Other promotion is performed by salesmen who work for the distributors.

Mr. Fogg provided some recent shipments as follows:
<table>
<thead>
<tr>
<th>Invoice - And Date</th>
<th>Consignee</th>
<th>Number of Cases of Minipor IV Filters</th>
</tr>
</thead>
<tbody>
<tr>
<td>B8925 3/14/84</td>
<td>Mt. Saint Holly Hospital</td>
<td>20</td>
</tr>
<tr>
<td>B8845 3/2/84</td>
<td>Stainless Hospital</td>
<td>80</td>
</tr>
<tr>
<td>B9045 3/28/84</td>
<td>Major General Hospital</td>
<td>60</td>
</tr>
<tr>
<td>B9051 3/29/84</td>
<td>VA Hospital</td>
<td>30</td>
</tr>
<tr>
<td>B9054 3/30/84</td>
<td>General Hospital</td>
<td>30</td>
</tr>
<tr>
<td>B9055 2/29/84</td>
<td>Molino Hospital</td>
<td>20</td>
</tr>
<tr>
<td>B9058 3/30/84</td>
<td>Hurt Hospital</td>
<td>30</td>
</tr>
<tr>
<td>B9069 4/2/84</td>
<td>Ritz Hospital</td>
<td>10</td>
</tr>
<tr>
<td>B9076 4/2/84</td>
<td>Cardio General Hospital</td>
<td>10</td>
</tr>
<tr>
<td>B9082 3/29/84</td>
<td>Heart and Lung Clinic</td>
<td>20</td>
</tr>
<tr>
<td>W8474 3/16/84</td>
<td>Monitor Hospital</td>
<td>20</td>
</tr>
<tr>
<td>D21606 3/30/84</td>
<td>St. Alchemy Hospital</td>
<td>15</td>
</tr>
</tbody>
</table>

The above invoices are attached as Ex. 25. The invoices are noted to reference the manufacturing (sterilization date. This date is ink stamped on each carton (case). This coding and invoice system will facilitate a recall, should one occur.
REFUSALS

There were no refusals during this inspection.

DISCUSSION WITH MANAGEMENT

At the close of the inspection, the FD 483, Inspection Observations, was presented to and discussed with Mr. John (NMI) Fogg, President. Dr. Paul M. Turner, Quality Assurance Manager, was also present during this discussion. Inspectional observations concerned five minor deficiencies in the device master record. Mr. Fogg stated the point #1, acceptance criteria for components, had already been corrected and gave me a copy of this document (see Ex. 8, Pg. 1). Mr. Fogg stated that the other deficiencies were simply oversights and could easily be corrected. No additional suggestions were given. One comment was made, which was that the firm discuss its proposed new EtO sterilization procedure with someone in the Center for Devices and Radiological Health, as this proposed procedure does not appear to have been commercially use. Mr. Fogg stated he believed a number of hospitals and small institutions were using this new EtO sterilization procedure, but was not aware of any manufacturer using the procedure.

SAMPLES

There were no samples collected during this inspection.

EXHIBITS

1. QC Manual re: policy & organization
2. QA manager responsibilities
3. QC manager responsibilities
4. Metrology manual
5. Examples of calibration standards traceable to NBS
6. List of components used to manufacture filters
7. List of component suppliers
8. Component sampling and acceptance plan
9. Blood filter sampling & acceptance plan
10. Component supplier agreements
11. Device master record operation sheets
12. Device master record
13. Sterility assurance procedures
14. LAL test procedures

15. Environmental air sampling procedures

16. USP/NF bubble point testing procedures

17. Device history record, blood filter, lot #00401, released 3/29/80

18. EtO residue study, 1976 & 1980

19. Safety/Toxicity study, 1976

20. EtO sterilization validation study, 1980

21. Letter, 2/1/84, from Acme Sterilizers

22. Shelf life study plan, 1976

23. Consumer complaints

24. Medical device complaint M-00210, dated 5/31/84

25. Invoices of 12 recent shipments

26. List of devices manufactured

27. Labeling for blood filters

ATTACHMENTS

1. CP 7378.830 Systems analysis report

2. CP 7378.830A Sterile device compliance program pages 2-10 & 15-18

Thomas E. Cardamone

Investigator 800

New York District

MODEL WARNING LETTER

CERTIFIED MAIL

RETURN RECEIPT REQUESTED

RESPONSIBLE INDIVIDUAL, TITLE
Dear (Addressee) ,

During an inspection of your firm located in (City, State) , on (dates) , our Investigator(s) determined that your firm manufactures (type of device) , (Name of device) are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed that these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Good Manufacturing Practice (GMP) for Medical Devices Regulation, as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Failure to conduct planned and periodic audits of the quality assurance program in accordance with written procedures. For example, no audits of the quality assurance program have been performed for at least 3 years.

2. Failure to investigate the failure of a device to meet performance specifications after a device has been released for distribution, and to make a written record of the investigation including conclusions and follow-up. For example, there are no records of failure investigations for Model , S/N , and Model , S/N , which were returned because they did not operate properly.

3. Failure to maintain device history records for Model to demonstrate that the devices are manufactured in accordance with the device master record.

4. Failure to immediately review, evaluate and investigate any complaint pertaining to injury, death, or any hazard to safety. For example, there is no record of the investigation of a report that a child's death associated with the use of Model at the Community Medical Ctr. on/or about Feb. 8, 1991.

Additionally, the above stated inspection revealed that your devices are misbranded within the meaning of Section 502(t)(2) of the Act, in that your firm failed to submit information to the Food and Drug Administration as required by the Medical Device Reporting (MDR) Regulation, as specified in 21 CFR Part 803. Specifically, you failed to submit an MDR report to FDA after receiving information which reasonably suggested that one of your commercially distributed devices may have caused or contributed to a death. The February 8, 1991, incident report from the Community Medical Center in which a child standing in a crib fell over, caught his head in a AY@ formed by the crib rail and end post, and died, should have been reported as a death.

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA 483 issued at the closeout of the inspection may be symptomatic of serious underlying problems in your firm's manufacturing and quality assurance systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be systems problems, you shall promptly initiate permanent corrective actions.

Federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, no premarket submissions for devices to which the GMP deficiencies are reasonably related will be cleared until the violations have been corrected. Also, no requests for
Certificates For Products For Export will be approved until the violations related to the subject devices have been corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to (Name), Compliance Officer, Food and Drug Administration,

(City, State & Zip Code).

Sincerely yours,

Updated 1/1/1997