Medical Device Manufacturers:
Guide to Inspections of Medical Device Manufacturers

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1 INTRODUCTION

The "Guide to Inspections of Medical Device Manufacturers" is a consolidation of information previously provided in the May 4, 1995 Compliance Program (CP), Inspections of Medical Device Manufacturers, CP 7382.830, Attachments A, B and E only. This guide was prepared by the Food and Drug Administration (FDA), Office of Regulatory Affairs (ORA) and the Center for Devices and Radiological Health (CDRH).

The new Quality System Regulation (F.R. vol. 61, No. 195, October 7, 1996) became effective on June 1, 1997. To implement the revised regulation CP 7382.830 has been rewritten and information relative to how to inspect a medical device manufacturer has been removed. The Compliance Program still contains information on when to do a directed inspection, the definitions of comprehensive and directed inspections, and other device specific policy requirements.

This reference is intended to be used in conjunction with the:

- Compliance Program Guidance Manuals for Medical Device Manufacturers (CP 7382.830 (GMP) and 7382.830A (Sterilization)),
- Investigations Operations Manual (IOM),
- Code of Federal Regulations, Title 21 (21 CFR) Part 820 Quality System Regulation,
- Compliance Policy Guides (CPG) for devices (beginning with the numbers 7124 and 7133), and

Other references include:

- the Safe Medical Devices Act (SMDA) of 1990 and the Medical Device Amendments of 1992,
- Medical Device Quality Systems Manual: A Small Entity Compliance Guide,
- The FDA Worldwide Quality System Requirements Guidebook for Medical Devices, and;
- other device specific guidance documents prepared by CDRH for the medical device industry.

These additional guidances are posted to the CDRH Internet World Wide Web Home Page at http://www.fda.gov/cdrh
2 GENERAL

The medical device Quality System/GMP Regulation (QS/GMP) is an umbrella GMP intended to cover all medical devices from dental resins to magnetic resonance imaging devices to In Vitro Diagnostics (IVDs) to some engineered tissues. The Quality System Regulation specifies general objectives (e.g. calibrated equipment, training, management responsibility, process and design controls) rather than methods, since one method would not be applicable to all manufacturers. In most cases, it is left to the manufacturer to determine the best method to attain these objectives.

Manufacturers should be able to defend their methods, procedures, etc. as being appropriate and adequate. Not all sections of the QS/GMP will apply to each manufacturer. Manufacturers must determine what sections of the QS/GMP apply to their specific products and operations. When a manufacturer decides that a section of the QS/GMP qualified by the term "where appropriate" does not apply, they are required to document their justification.

Investigators should use good judgment when conducting a medical device QS/GMP inspection. They need to:

a. assess whether the manufacturer has the required written procedures,
b. is following those procedures and,
c. has documented evidence that those procedures, methods, etc. are adequate given:

1. the size of the firm,
2. the complexity of the device(s) being produced and,
3. the relative risk to users if the device does not meet its finished product specifications or the manufacturing facility is not operating in a state of control.
3 PRE-INSPECTIONAL ACTIVITY

Prior to the start of any medical device inspection, the factory jacket or establishment history of the firm should be reviewed. Special notice should be made of the previous inspectional findings and subsequent correspondence between the firm and FDA; of any MDR or consumer complaints where it was determined that follow-up would occur at the next inspection; and of any notifications of recalls since the last inspection.

The following on-line databases should be queried:

a. CDRH Information Retrieval System(CIRS) - for Medical Device Reporting (MDR) data (MAUDE), Registration and Listing data and 510(k) and PMA summary data (OSCAR);

b. MDRAPSY for MDR data prior to October 1996.

These databases are accessible to users with individual accounts. Accounts can be requested through the district or regional CIRS liaisons or from DEIO/Denise Dion (301) 827-5645 for MDRAPSY.

MDR data that is most useful in preparing for an inspection of a medical device manufacturer includes specific MDRs for that manufacturer (i.e. query by firm's short name) for the time frame since the last inspection; or MDRs relative to the generic devices manufactured by that firm (i.e. query by product code) for some reasonable time frame. This data assists the investigator in determining possible problem areas in the manufacture, or design, of the device, or lot or batch specific issues. This data should be used to focus the inspection.

The firm's reported registration and listing data should be verified during any GMP inspection to assure there have been no changes and the registration and listing data was accurately reported. Changes or inaccuracies should be immediately reported to the district medical device registration and listing monitor. See also Field Management Directive (FMD) 92.

510(k) and PMA data assists the Investigator in determining what devices the firm is manufacturing and whether any new devices have been designed or changed since the last inspection. This data is useful in focusing the inspection on new or changed devices as well as devices that are higher risk devices, i.e. class II or III versus class I.
4 GMP INSPECTIONAL STRATEGY

CP 7382.830 describes the inspectional strategy to be used. This Guide discusses how to perform a directed inspection, or a comprehensive inspection. It also discusses inspections of small manufacturers. In brief, all inspections of medical device manufacturers are to be directed inspections, with the exception of OAI follow-up inspections, which are to be comprehensive inspections.

4.1 Preannouncements, 483 Annotations, Post Inspectional Correspondence:

ORA conducted a pilot program, Medical Device Industry Initiatives, in FY 96 through the first quarter of FY 97 which encompassed preannounced medical device inspections, annotated FDA 483s and post-inspectional correspondence for NAI and VAI inspections. The initiatives have been implemented on a permanent basis. The instructions for preannouncement, including the criteria to be used, 483 annotations and post-inspectional letters for NAI and VAI inspections are included as Attachment A to this guide.

One of the purposes to preannouncing is to assure that the appropriate records and personnel will be available during the inspection. Therefore, it is important you communicate to the firm the purpose of the inspection and a general idea of the records you may wish to review. If you find neither the appropriate personnel or records were available, please note this in your Establishment Inspection Report (EIR). This data may be used by the district in the future when considering whether this firm should be eligible for preannounced inspections.
5 DIRECTED DEVICE INSPECTION

With the finalization of the new Quality System/Good Manufacturing Practices (QS/GMP) regulation, FDA formally recognized a new systems approach to regulating medical devices. It is FDA's intention to use this same approach when conducting inspections. A systems level approach to conducting inspections means taking a broader view. A great deal of flexibility has been written into this regulation, which means Investigators need to more fully concentrate on the firm's state of compliance at the system level. How best can that be done?

It is important to focus the inspectional effort on those systems that will provide the firm with information regarding failures in their process, the actual device design, their raw materials, or their employee training. These systems include: complaints, MDRs, servicing, product acceptance, change control, process validation, design control, and internal audits. Problems or failures in these areas are most likely to result in faulty or hazardous devices being released into commercial distribution. These areas may also serve as first indicators for the firm that nonconforming product may have been distributed. Therefore, a firm's system for recognizing failures and implementing corrective and preventive actions is also a key system to assure a firm meets its own and FDA's requirements for quality medical device design and manufacturing.

Because of this, FDA uses a directed inspection approach for all surveillance and pre-approval inspections. Generally, more comprehensive inspections are done only after a firm has been found to not be in substantial compliance based on a directed inspection, i.e. a follow-up inspection of an OAI (Official Action Indicated) inspection.

The purpose of a directed inspection is to look at those areas that are of the greatest concern in assuring that a firm is not designing, manufacturing or distributing hazardous or non-conforming devices. These systems should be inspected to assure that they conform to the QS/GMP requirements. The information contained in these systems may also indicate there are problems in designing, manufacturing, servicing, training, testing, labeling, packaging, etc. They may indicate that hazardous or nonconforming devices have been manufactured and/or distributed. This type of information should be used to help focus the inspection on a particular device, lots or batches of devices, or on particular manufacturing processes.

As a general rule, the Investigator should select devices for inspectional coverage which, because of what they are made of or how they are made, have the highest potential for problems that could result in the design, manufacture and/or distribution of unsafe or unreliable devices. This rule should be applied when there is no evidence in the complaint, MDR, testing or servicing records of specific problem devices. If there are recall or MDR issues already known regarding a particular device, or a device manufactured by the firm has been the subject of prior warning of non-compliance, then these devices should be the focus of your inspection. Once a device has been selected, the inspection should focus on those significant systems that are meant to assure the manufacture of safe and reliable devices: process validation, component acceptance, change control, design control, and control of nonconforming product.

Evidence of nonconforming products should be viewed as an indicator of noncompliance with the QS/GMP. As an inspectional function, this is the best starting point to inspect the overall quality system.
For example, if the firm does not have the documents and data related to our reports of non-conforming devices or of devices that caused injury or death (MDR) this would be a significant non-compliance with the QS/GMP.

Inspectional observations should focus on cause and effect to link observed problems to the potential of manufacturing nonconforming product(s). Start with the evidence that an unsafe and/or unreliable product was or may have been distributed as indicated in MDRs, complaint records, service records, incomplete corrective and preventive actions, and distribution records for release of nonconforming products. The inspection should then be focused on those QS/GMP systems that have a high probability of causing the problems indicated by the complaints, MDRs, etc.

Inspectional observations relative to those systems should be related to noncompliances of significant risk. It should also be determined whether other devices with these potential problems would result in the distribution of an unsafe or unreliable product.

Any observed nonconformance to written procedures should be documented with a copy of the written procedure and additional observations to show the nonconformance is not just a one time occurrence. If observations are related to people dependant processes, the inspection should provide sufficient documentation to show the problem to be a training issue, the use of unqualified people or process validation related problems.

Lastly, the QS/GMP places major emphasis on the role of management and management responsibility. The inspection process should show through the firm’s written documentation the role of management in the quality process to prevent the design, manufacture and distribution of nonconforming products.

5.1 Complaint Handling System - 21 CFR 820.198

This should be the beginning point of every inspection to determine whether the firm has received complaints of possible (or potentially) defective devices. The QS/GMP regulation requires all complaints be reviewed, evaluated and maintained by a formally designated unit. This unit could be one appropriately trained individual, or a department which is staffed with appropriately trained individuals. This unit must decide whether an investigation of the complaint needs to be performed.

Under the QS/GMP there continues to be no requirement that all complaints be maintained in one file. However, firms are now required to have written procedures for processing complaints. To assess the adequacy of the written complaint handling procedures, only complaints received after June 1, 1997 should be reviewed. However, the review of complaints to determine which devices the inspection should be focused on should not be limited only to those complaints received after June 1, 1997. The complaint file(s) must contain all complaints including those open or still under investigation.

Typically, manufacturers will keep complaints in a customer file, product returns/credit file, service file, warranty file, medical file, or legal file. The inspection should ascertain what files are maintained that meet the definition of a complaint (21 CFR 820.198). By placing complaints in different files, manufacturers may not have noted instances of repeated component/device failures with a common
cause. Ask the firm if it trends or performs other analyses of complaints. If no trending or problem identification is done, then the inspection should begin with a trending of the complaints.

**NOTE:** The actual complaints may provide leads in identifying product defects. Deficiencies in complaint handling practices may result in lost complaint data essential to identifying product defects, and possibly quality system problems, which have not been adequately corrected by the firm. Possible corrective actions may include recall, and/or change in the design of the device, and/or change in the manufacturing process or quality system.

Review and analyze the complaints to identify existing and/or potential causes of nonconforming product or other quality problems by grouping similar products, failure modes, and failure site (use, location) for possible user or environmental related problems.

Potential environmental factors that could contribute to the failure of a device include the area of the country, weather, use factors, electromagnetic interference, vibration, shock, etc.

Determine if the firm has performed sufficient complaint investigation, or to the extent possible, to confirm the reported failure mode.

Determine the identity and qualifications of those who review complaints. Ascertain the basis for determining significance of complaints and how follow-up is conducted. Determine if oral or telephone complaints are documented.

Some firms file complaints under other names, such as "Trade Inquiries," "Technical Assistance," "Customer Contacts," "Service Requests" etc., while others make a distinction between physical/mechanical and medical complaints. Make sure all complaints are adequately covered and reported.

When a manufacturer claims to have received no complaints, determine if provisions have been made for the review and investigation of complaints when received. Determine who has been assigned the responsibility to evaluate them when and if they occur.

**5.1.1 Establish and Maintain Complaint Handling Procedures - 21 CFR 820.198(a)**

The firm must have written complaint handling procedures to process information in a uniform and timely manner. Indicators that the firm may not be in compliance would be shown in the firm's failure to pursue additional follow up to determine some or all of the following complaint information:

a. Identification of the complainant, including address and phone number and situation where reported event occurred.

b. Identification of complaint product to the extent necessary to identify the specific device history record for the manufacture of the implicated product.
This would be the lack of a model and serial number where one or both are necessary and the firm failed to try to obtain the information.

c. Information needed to determine time to failure and/or if the product has failed within its warranty period. This would be the lack of a beginning use or failure date (for IVDs - the expiration date).

d. Information to determine cycle to failure if the product's life is determined by cycle of use and not time. This would be failing to obtain how many times a mechanical device may have been used when the device has a built-in counter.

e. Information relative to contributing factors to the reported failure mode.

An example of this would be failing to obtain information about additional devices in use at the time, and the electrical environment during the reported failure that could be due to an Electromagnetic Compatibility (EMC) problem.

5.1.2 Determining Whether An Investigation Is Necessary - 21 CFR 820.198(b)
The firm should evaluate complaints thoroughly to determine whether an investigation is necessary. Indicators that the firm may not be in compliance would be shown by:

a. A history of one or more similar failure modes and has not investigated to confirm the reported failure mode.

b. The complaint records lack the reason for not investigating and/or the name of the individual responsible for the decision not to investigate.

If the firm states it has never received complaints and because of this it does not need a complaint handling system, it should be cited on the FDA 483 for failure to have a complaint handling system.

5.2 MDR Regulations - 21 CFR 803
Remember when reviewing complaints to check for MDR reportable events. The Compliance Program requires an MDR inspection every time a GMP inspection is made of a medical device manufacturer. CDRH has included in the Compliance Program guidance for evaluating a manufacturer's compliance with the requirements of the revised (July 31, 1996) MDR regulation.

The Establishment Inspection Report (EIR) must state that complaints, service records, etc. were reviewed for MDR reportability, that the firm's MDR procedures were reviewed and whether the firm was found to be in compliance with the MDR regulations. Observations related to the MDR regulations should be noted on the FDA 483 or discussed with management as appropriate.
For further guidance on MDRs, see CP7382.830 and the guidance manual dated March 1997 issued by CDRH/Division of Small Manufacturer's Assistance (DSMA), "Medical Device Reporting for Manufacturers"

5.3 Establish and Maintain Procedures for Performing and Verifying that the Servicing Meets Specified Requirements, and for Analyzing Reports - 21 CFR 820.200(a) and (b)

Manufacturers must analyze service reports, and where necessary, with appropriate statistical methodology in accordance with 21 CFR 820.100 (e.g. frequency distribution charts, Pareto analysis or other analytical methods). Documentation for this should be established under corrective and preventive action in accordance with section 21 CFR 820.100. A determination should be made as to whether the firm has an adequate system in place for screening repair and service requests to assure whether any of these meet the definition of a complaint. Service reports initiated as a result of a complaint must be cross-referenced in the complaint handling system. NOTE, every service report is not necessarily a complaint.

5.3.1 Determining MDR-Reportable Service Reports - 21 CFR 820.200(c)

Remember when reviewing service records to also check for MDR reportable events. Any service report that represents an event which must be reported to FDA under part 803 or 804 of the MDR regulation must automatically be considered a complaint and receive appropriate follow-up under the requirements of section 21 CFR 820.198.

5.4 Corrective and Preventive Actions - 21 CFR 820.100

It should be remembered the complaint section of the QS/GMP regulation (21 CFR 820.198(b)) refers to all complaints, whether or not a complaint represents a possible failure of the device. 21 CFR 820.198(c) requires all possible failures of devices to be investigated to determine whether the failure can be confirmed and/or cause of the failure can be determined. Once the failure is confirmed as an actual failure of the device, the Corrective and Preventive Actions section of the QS/GMP Regulation (21 CFR 820.100) takes effect. It is important to remember that at times trending or continual monitoring of complaints for specific failures can be a corrective and preventive action. This is especially true when a firm cannot determine the cause of the failure.

A determination must be made as to whether the firm has established procedures for implementing corrective and preventive action.

Determine if the firm screens repair and service requests and conducts trend analyses to identify premature failures within the warranty period, and to detect problems with particular components, subassemblies, or design.
Any product failures within the warranty period are likely to be product design or GMP related. For example:

a. Product design related issues may be those related to electrical safety, EMC, consistent user error or robustness of the product to packing, handling, storage and shipping.

b. GMP related issues are validation of assembling processes, screening and receiving, and in-process or finished device acceptance.

Review records for investigations to identify common failure trends (e.g., by component, subassembly, manufacturing error, or employee training). Compare these trends with corrective action documentation.

These common failure trends may provide clues to which areas or products to focus on during the inspection.

Your inspection should include detailed inspection of documents maintained under the requirements of 21 CFR 820.100, Corrective and Preventive Actions. In particular, you should focus on reliability issues that have not been documented for corrective and preventive actions. The continued distribution of devices with a known problem should be noted on the FDA 483 (or DCIS report for design problems.)

5.4.1 Analyzing Quality Problem Information

For devices in production, the manufacturer should be analyzing its quality problem information (e.g. in-process failures, complaints, field service reports, etc.) with appropriate statistical methodology where necessary to detect recurring quality problems. Examples of acceptable statistical methodology include statistical process control (SPC), periodic frequency distribution analysis and other methods of data trend analysis. Reference Juran "Quality Control Handbook" for examples of acceptable statistical quality control methods.

5.4.2 Analyzing Service Records

Service records are a significant source of possible failure data for serviceable devices to identify possible (or potentially) defective devices. Caution should be taken when reviewing service data to separate out routine maintenance (sometimes referred to as preventive maintenance) from servicing requested by the customer to a correct a problem, or that required by a "service bulletin" issued by the manufacturer to correct a problem. Such problems may indicate that possible or potentially defective devices were produced as the result of design or manufacturing problems.

Some examples of routine and non-routine service are:

a. Servicing performed at time of a scheduled maintenance per contractual agreements or per device labeling would be considered routine. Although this servicing is considered routine, the records may contain unscheduled and non-routine maintenance such as a convenient time to perform a product recall or market correction.
b. Non-scheduled, under warranty, performing product recalls or market withdrawals are some examples of non-routine servicing.

The records reviewed should start from the most current and work back toward a 24 month maximum time period. The selection of the number of service records for review is governed by the form of record availability (electronic or hard copy) and the experience and skill of the Investigator in reviewing a large volume of hard copy or electronic records.

Determine if the firm has analyzed the service records to identify existing and potential causes of nonconforming product or other quality problems. Before reviewing service records, review any trending information that the firm has performed and review any corrective actions the firm may have already taken.

The review of service records should be done by grouping “field of information” to determine any potential trends for possible defective devices. The grouping of data is performed by sorting the data by different fields and combination of fields to determine any relationship of product failures to product design and/or manufacturing processes.

Suggestions for grouping would be by model, serial number (lot or batch number), or component failures to focus the inspection to possible product design or manufacturing problems. The serial numbers and corresponding device history records could point to manufacturing problems with out-of-specification components, inadequate employee training, acceptance testing problems, etc.

Serial number grouping can also reveal repeat failure modes indicating an inadequate corrective action. A common repeat service action is to repeatedly replace computer processing units (CPU) with the same failure mode recurring. This is a common ineffective fix when the problem is software related but the symptom is always computer related.

Grouping by service site - area of country, type of user and time of failure - could point to product design defects. For example, if the failures appear to be related to dry climate areas, the device may not have adequate protection from Electrostatic Discharge (ESD) damage. If the user type is emergency medical service (EMS), the device may not be robust enough for vibration, shock, electromagnetic compatibility (cell phones, radio transmissions, etc.) and other environmental stresses encountered with EMS services.

5.5 Nonconforming Product - 21 CFR 820.90

A determination must be made as to whether there are any instances of release and distribution of lots that failed to meet any specifications.

This could be done by examining device history records and in-process control records for any lots, or portions of lots (including components or raw materials) that have been rejected during either in-process or finished device inspection for failing to meet any or all of the product’s specifications. Any distribution of these out-of-specification products should be reported and documented. When the nonconformance was reviewed by a material or engineering review board, evaluate the rationale used
to justify continued use of nonconforming raw material, component, in-process product or sub-assembly.

Records must be examined to determine whether any lots that have failed specifications were reworked, and whether this reworking is adequate to assure specifications will be met without affecting the safety or performance of the device.

A high rate of rework would also provide strong evidence that the manufacturing process is not operating in a state-of-control.

A review should be made to determine if all sampling plans for inspection and rework are based on an acceptable statistical rationale and technique. (Mil. Std. ANSI/ASQC, etc.)

Records maintained under 21 CFR 820.90 for nonconforming product and product rework information maintained within device history records should be analyzed for failure trending data.

The inspection of this data for repeat component failures may further connect the problem to a manufacturing step, a work station or to one or more employees.

5.5.1 Control of Nonconforming Product - 21 CFR 820.90(a)
Determine if the manufacturer has established procedures to "control" nonconforming product. The procedure must "address the identification, documentation, evaluation, segregation, and disposition of nonconforming product." The procedure must also include a "determination of the need for an investigation." The evaluation and any investigation must be documented, including documented explanations for not performing an investigation. Documentation should also include how nonconformances will be trended and/or monitored.

5.5.2 Nonconformity Review and Disposition - 21 CFR 820.90(b)(1)
Review all records for the proper disposition of nonconforming products for assurance that use of nonconforming product has not resulted in the distribution of defective devices. The distribution and justification for concessions (allowance to use otherwise nonconforming product, often done through a Material Review Board) must be documented and based on scientific evidence. Concessions should be closely monitored and not become normal practice.

Deficiencies would include a lack of scientific evidence for justification of the concession. If a concession resulted in a change of product specifications (form, fit or function), the change should be evaluated for possible 510(k) submission. At a minimum, a risk analysis should always be considered for any changes.
5.6 Evaluation of Procedures for Change Control - 21 CFR 820.30(i) and 820.70(b) and Device Master Record (DMR) - 21 CFR 820.181

A determination must be made as to whether the firm's device design and/or process changes are, or may be, contributing to defective devices. There are several ways of making this assessment, for example;

a. Review any changes to the device design and/or process that may have occurred as a result of complaints, servicing/repairs, failure investigations, in-process/finished device inspection, or rework/ re-inspection. Instances of such changes can be determined by examining the change control documentation as well as by revisions to existing procedures, DMRs or deviation reports associated with Device History Records (DHR). If changes have been made to either the device design or the device manufacturing process, determine whether they have been adequately validated, and/or where appropriate, verified.

b. Determine if there are a series of change orders (found by reviewing the DMR and various engineering drawings) for the same device which are intended to sequentially correct the same or similar problems.

This, or complaints received after a design change, may indicate the original change was not effective or was not adequately verified and validated and that subsequent changes have been, or are being, made to correct the problem.

A memo, signed by the Directors of the Office of Regional Operations and Office of Enforcement, dated June 6, 1997, regarding when to cite changes on the FDA 483 for the transition year (June 1, 1997 - May 31, 1998) is included as Attachment B to this guide.

All changes relative to the device design (this includes all changes for software that is part of the device, is the device and some automated design testing software) should be documented on the Design Control Inspectational Strategy (DCIS) Report -see CP 7382.830, Attachment F.

5.7 Process Validation - 21 CFR 820.75

The QS/GMP does not require the validation of all manufacturing processes. Before inspecting a manufacturing process for process validation, it is important to determine if the results of the process cannot be fully verified by subsequent inspection and test. The lack of a subsequent inspection and test should be stated in the EIR along with any process validation issues.

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

Prospective process validation is validation conducted prior to the distribution of either a new product, or a product made under a revised manufacturing process, where the revisions may affect the product's characteristics.
Retrospective process validation is validation of a process for a product already in distribution based upon accumulated production, testing and control data.

Generally, process validation is a pre-production activity. Prospective validation includes considerations made before a new product is introduced, or when there is a manufacturing process change which may affect the product’s characteristics. The validation program must be planned and documented, and the validation results must be documented and maintained.

Installation qualification should be conducted for equipment used in a validated process to assure that the equipment has been properly installed, meets the device manufacturer’s specifications and requirements for it, and is capable of operating in the range required for the process being validated.

During installation qualification, equipment maintenance and calibration schedules and procedures should be established. Equipment should be calibrated before and after process validation to determine whether the equipment remained in calibration during the entire process validation study.

If the equipment is found to be out of calibration at the end of the study, the validity of the results is called into question. Installation qualification does not have to be performed again if it was recently done for a previous validation. When equipment is moved, a new installation qualification should be performed.

The requirement for equipment qualification can be traced back to 820.70(g). Installation qualification is essential for successful process validation.

The process must be developed before it can be validated. From time to time we see manufacturers who try to validate processes before they have completely developed them and established process parameters. It is impossible to validate a process (i.e. show that it consistently operates within established parameters and produces results or products that meet specifications) until the process is fully developed, and appropriate parameters have been established. The requirement to develop the process can be traced back to 820.70(a). It is important to remember that validation is dynamic and specifications and parameters may be changed as a result of the validation efforts. These changes would need to be validated.

Finally, the product should be qualified. In other words, the product produced by the validated process should be checked to determine whether the process has had any adverse effect on the product or its performance.

For example, radiation sterilization may result in degradation of plastic devices which can lead to premature failure. Or, certain product specifications may have been changed to make the product easier or less expensive to manufacture, but these changes may adversely affect product performance. Product qualification for process validation may take place during design validation.

Retrospective process validation may be used, if adequate, for products which may have been on the market without sufficient pre-production process validation. Extensive review of manufacturing and
assembly process data, along with product testing, may be used as a type of validation for devices manufactured individually or on a one time basis.

Validation should be performed (as applicable) for processes such as sterilization operations (steam, dry heat, ETO, radiation, filtration, aseptic fill), manufacturing operations (lyophilization, molding, soldering, machining, blending/mixing, water purification systems), environmental control systems (clean rooms and laminar air flow units), test methodology, and packaging/labeling operations.

Determination should be made as to whether the firm's processes are or may be contributing to defective devices. There are several ways of making this assessment, for example:

a. Process validation information should be reviewed to identify defect characteristics and rate of expected defects of each characteristic for the finished product. If the rate of defects are found to be exceeded during in-process or finished device acceptance, the process(es) may be out-of-control or were not properly validated.

b. Review first and last article test results for continuous processes such as extrusion or injection molding, automated soldering, automated filling lines, automated testing, etc. which may show test failures of the last test article.

If a last article test was found out-of-specification and the firm accepted the products produced within the bracketed period, the firm may be accepting out-of-specification product for further manufacturing or distribution. Refer to the section of this guide on nonconforming product for guidance on inspecting product concessions.

The testing of the first and last article is to bracket a processing period to show the first and last article and all articles produced between the two tests met specification. If last article failures are found, the process may not be capable of operating in a steady state of control for the time period between the first and last article testing. Process validation, equipment control parameters, environmental (temperature and humidity) controls and condition of components (temperature and moisture content) should be questioned.

The inspection must determine whether adequate prospective or retrospective validation of the manufacturing process has been performed. Validation must ensure the quality of the product will be maintained if the process is controlled within established parameters and that the validation, either prospective or retrospective, has addressed the limits of these parameters.

The firm should be able to document they can control the process within their established limits, e.g. the high and low process parameters should be tested to determine whether the process can be controlled at these limits and whether the product will still meet specifications if the process is operated at these limits. Note: It is not necessary for the firm to run the process at the high and low limits for each of the validation runs. They do need to be able to show that operating the system within the established limits will produce acceptable product. Operating the process at established limits is a form of stress testing. Stressing the system does not require causing the system to fail.
Pay attention to the process parameters: temperature, humidity, tensile strength, viscosity; verify the manufacturer has included all the necessary parameters in the processing procedures. Validation, depending on the scope of the operation, can cover all aspects from the selection of components to various manufacturing processes to end-product testing.

There are special documentation requirements for validated processes. In particular, documentation is required to show what equipment was used in the process validation efforts to assure that equipment routinely used in production is the same as the equipment used in the process validation study for that process. Changes in equipment are cause for revalidating the process.

Operators of validated processes should be documented to facilitate checks to assure that operators are qualified to operate validated processes.

All operators should be qualified for their work, but because the results of validated processes need not be fully verified, the need for qualified operators is especially important to assure that validated processes are properly conducted and controlled and produce results or products that meet specifications.

Review and evaluation of process changes and deviations should be documented to show whether revalidation is necessary and if not, why not. It is important to remember that the manufacturer needs to maintain a validated state. Any change to the process, including changes in procedures, equipment, personnel, etc. needs to be evaluated to determine the extent of revalidation necessary to assure the manufacturer that they still have a validated process.

As noted above, QS/GMP regulations do not require all medical device manufacturing processes to be validated Per 21 CFR 820.75. However, where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated. Questions regarding whether a process needs to be validated can be directed to CDRH/Office of Compliance or via the ORA Banyan mailbox: validation@deio@fdaorahq.

5.8 Components - 21 CFR 820.50 and 820.80

A determination should be made as to whether the firm is or may be producing nonconforming devices by using nonconforming components.

There are several ways of making this determination:

a. Review of complaints, service and failure investigation documents show root causes of defective devices determined to be nonconforming components.

b. Review of temporary authority (deviation authority) or other documents authorizing the use of nonconforming components.

c. Determine if the firm is using appropriate statistical rational and technique for acceptance sampling and testing of components.
d. Particular attention should be paid to custom components and those components that would require special handling or storage to maintain their integrity. Be wary of situations where a manufacturer has relaxed specifications because the supplier could not meet the original specifications.

e. Determine if the test and/or screening parameters used for component acceptance based only on certificate of conformance will produce devices meeting finished product specifications.

f. Where a manufacturer uses Just In Time (JIT) component acceptance, and relies on component vendor audits in place of incoming component inspection, review the manufacturer's audit schedule and audit procedures. Pay special attention to the vendor's rejection rate.

5.9 Quality Audits - 21 CFR 820.22

The quality audit is the foundation of the quality assurance program. Determine if the manufacturer has a written procedure for conducting quality audits and how often these audits are conducted. It is recommended that the time between audits not exceed a 12-month period. More frequent audits may be recommended if the firm has a serious GMP problem.

The agency's policy relative to the review of quality audit results is stated in CPG 7151.02. This policy prohibits FDA access to a firm's audit results. Under the QS/GMP, this prohibition extends to reviews of supplier audit reports and management reviews. However, the procedures and documents that show conformance with 21 CFR 820.50, Purchasing Controls, and 21 CFR 820.20(3)(c), Management Reviews, are subject to FDA inspection.

Quality audits should consist of a formal, planned check of all elements in the quality system. They are NOT product audits. Such audits must be conducted using adequate detailed written procedures by appropriately trained individuals. If conducted properly, a quality audit can detect program defects and, through 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 is incomplete and there is no assurance the manufacturer is consistently in a state-of-control.

Evidence of inadequate auditing may exist without gaining access to the written audit reports. This evidence may be obtained by relating the audit program to deficiencies observed in complaint files, change control and/or calibration, or other problems in quality systems. If significant quality system problems have existed both before and after the firm's last self audit, then you should critically review the written audit procedures. The audit procedures should cover each quality system, and should be specific enough to enable the person conducting the audit to perform an adequate audit. The auditors must be adequately trained. If it is possible to interview an auditor, ask how the audits are performed; what documents are examined; how long audits take; etc.

Audits should be conducted by individuals not having direct responsibility for matters being audited. In one-person and very small firms, where hiring an outside auditor to meet this requirement would be impractical or overly burdensome, self-audit may be acceptable and the auditor need not be
independent. Consult with CDRH or the Division of Emergency and Investigational Operations as necessary. If there are significant FDA-483 observations, and independent audits are being performed, but deficiencies are apparently not being identified by the auditor, then an FDA-483 should contain an observation indicating a lack of adequate audits.

Determine whether corrective action by upper management is being taken. Auditors may be asked if they observed any of the ongoing GMP deficiencies during their prior audits (ongoing GMP deficiencies may also be identified by reviewing prior FDA-483’s). If the answer is yes, check the written audit schedule, if available, to determine if follow up audit is scheduled for the deficient areas. Also, check the written audit procedure for instructions for review of audits by upper management, and re-audit of deficient areas. A failure to implement follow-up corrective actions, including reaudits of deficient matters may be listed as a GMP deficiency on the FDA-483.

**NOTE:** Reaudits of deficient matters are not always required, but where one is indicated, it must be conducted. The reaudit report should verify the recommended corrective action(s) was implemented and effective.

The QS/GMP regulation (21 CFR 820.180(c)) requires a manufacturer to certify in writing, whenever requested to do so by an Investigator, that audits and reaudits have been conducted. You should consult with CDRH (HFZ-305) through your supervisor/team leader, etc. prior to requesting such certification.

### 5.10 Design Controls - 21 CFR 820.30

From June 1, 1997 through May 31, 1998, all GMP inspections of medical device manufacturers will include an assessment of the firm's design controls utilizing the Design Control Inspectional Strategy (DCIS) included in CP7382.830 Attachment F (also available electronically on CDRH's home page and the Banyan Bulletin Board under DFI Live, Medical Device Reference Materials.) This strategy constitutes the method of conducting an inspection of design controls.

For this first year, a transition period for design controls, no observation relative to design controls (or changes or software - see Moratorium memo dated June 6, 1997, Attachment B) will be included on the FDA 483 or used to support any regulatory action. If the design of a device is found to be unsafe or ineffective for its intended use, FDA can take action under other sections (non-GMP) of the Food, Drug and Cosmetic Act (FD&C Act).

Observations relative to design control requirements, changes and software will be recorded on the DCIS report. The DCIS report will become part of the firm's EIR and will be available under Freedom of Information (FOI). Portions of the report may be purged to protect confidential and trade secret information. Therefore, it is important for the Investigator to identify which portions of the DCIS report the manufacturer considers confidential to assist the agency in its FOI determinations.

Do not collect documents or records, during the transition year (June 1, 1997 - May 31, 1998) to document areas in need of improvement that are included on the DCIS report. Do not collect documents or records merely to assist you in writing the DCIS report. You will need to take good notes to assist you
with this task or write the responses, etc. directly onto the automated report. Exception is the general
design control planning procedure, if available, as noted on the Design Control Inspectional Strategy.

The listed Areas in Need of Improvement should be written in the same manner required for an FDA 483
observation.

5.11 PMA Devices - 21 CFR 814.20 and 814.39(a)(4)
If any PMA devices are manufactured at the facility being inspected, determine whether this
manufacturing site was approved in the original PMA or a PMA supplement, even if only partially
manufactured at the inspected site. Report discrepancies in the EIR and notify CDRH, HFZ-306 (Field
Programs Branch).

5.12 Medical Device Tracking - 21 CFR 821
A determination must be made as to whether the firm manufactures any devices required to maintain
device tracking data (see CP 7382.830 Attachment D). If so, determine whether the firm has device
tracking procedures in place and if they are adequate to assure each device required to be tracked will
be tracked to the actual end user, i.e. the patient. One method to do this would be to obtain a list of
devices distributed during a given time frame and then look for those devices in the tracking database.

If there is a complete lack of a tracking system, this should be cited on the FDA 483. Other observations
should be discussed with the firm's management and reported in the EIR. The EIR must indicate whether
or not the inspected firm makes any device subject to the device tracking requirements. If so, the EIR
must include a statement that the firm's procedures, tracking database, etc. were assessed for
compliance to the

Medical Device Tracking Requirements (21 CFR 821). All FDA 483s or EIRs with medical device tracking
observations must be sent to CDRH/Office of Compliance, Field Programs Branch (HFZ-306).
6  COMPREHENSIVE DEVICE INSPECTION

A comprehensive inspection is required to be done when performing a compliance inspection (OAI follow-up inspection) of a firm. It must include all of the items discussed under Directed Device Inspections as well as a determination of whether all previous FDA 483 observations have been investigated and corrective action has been implemented. Additionally, all other quality system requirements in the QS/GMP regulation should be inspected for compliance.

6.1  General Provisions - 21 CFR 820.1 and 21 CFR 820.3

All requirements of the QS/GMP regulation apply equally to manufacturers, large and small, foreign and domestic, of finished medical devices. Manufacturer includes any person or firm that designs, manufactures, fabricates, assembles, or processes a finished device. Remanufacturers (performs any act to a finished device that significantly changes the device's performance or safety specifications or intended use) must also comply with the QS/GMP regulation. Currently, they do not apply to refurbishers or third-party servicers (performs any act outside of the control of the original equipment manufacturer (OEM) that only restores the finished device to its original performance or safety specifications or intended use, or does not significantly change the original performance or safety specifications or intended use).

6.2  Quality System Requirements - 21 CFR 820.5 and 21 CFR 820.20

All manufacturers of medical devices are required to establish and implement a quality system tailored to the device manufactured. Each manufacturer must prepare and implement all activities, including but not necessarily limited to the applicable requirements of the QS/GMP, that are necessary to assure the finished device, the design process, the manufacturing process, and all related procedures conform to approved specifications.

The term "quality system" as specified in the GMP encompasses all activities previously referred to as "quality assurance" which were necessary to assure the finished device meets its predetermined design specifications.

This includes assuring manufacturing processes are controlled and adequate for their intended use, documentation is controlled and maintained, equipment is calibrated, inspected, tested, etc. Some manufacturers may use the terms "quality control" or "GMP Control" or "quality assurance" instead of quality system. It doesn't matter what term is used as long as the quality system concept is understood and implemented. Historically, "quality control" has meant inspection and test which, although the primary mechanisms for detecting defects, only set aside nonconforming product and do not prevent the deficiency which caused the defect. Quality assurance activities are intended to prevent the production of non-conforming products and include quality control activities. A quality system applies to the organizational structure, responsibilities, procedures, processes and resources for implementing quality management. The GMP is based on this umbrella concept of a quality system and is designed to prevent the design or production of nonconforming product. A manufacturer's implementation of the QS/GMP is implementation of a quality system.
One aspect of a quality system is that it will identify, recommend, or provide solutions for quality problems and verify their implementation, as stated in 21 CFR 820.100.

Trend analysis is a method of complying with this QS/GMP requirement. Process and product accept/reject data collected by the firm through their documented systems, along with the complaint system, can be used in identifying conditions or situations which might not be apparent, or may be dismissed as isolated incidents. Once identified, measures can then be implemented to control or eliminate their recurrence.

Investigators should not make general FDA 483 observations that a manufacturer does not have a quality assurance system. If an adequate response is expected from the manufacturer the charge must be more specific and point out the controls that are missing or believed inadequate.

The firm must have a written quality policy. Management with executive responsibility (has the authority to establish and make changes to the company quality policy) must assure the policy is understood and implemented at all levels of their organization. The policy does not need to be extensive. Some of the best policies are only one to two sentences in length. Personnel are not required to be able to recite the policy but they should be familiar with it and know where to obtain it.

The firm’s organizational structure must be adequate to ensure devices are designed and manufactured in accordance with the QS/GMP. The organizational structure should ensure the technical, administrative, and human factors functions affecting the quality of a device are controlled. These functions may involve hardware, software, processed materials or services. All such control should be towards the reduction, elimination, or ideally, the prevention of quality nonconformities.

Manufacturers must assure personnel involved in managing, performing or assessing work affecting quality have the necessary independence and authority to perform those tasks. Organizational freedom or independence does not necessarily require a stand-alone group. However, the responsibility, authority and independence should be sufficient to attain the firm's stated quality objectives.

Adequate resources must be available for the quality system to assure the firm's stated quality objectives can be achieved. Resources include monetary, supplies, etc. as well as personnel resources.

The firm must appoint a management representative who is responsible for ensuring the quality system is effectively established and maintained and who will report on its performance to management with executive responsibility for review. Management with executive responsibility is required to periodically review the quality system for suitability and effectiveness. The review shall measure the firm's quality system against the QS/GMP and the firm's own stated quality objectives as defined in their quality policy. Both the appointment and the reviews must be documented.

There must be written procedures for conducting these reviews. As stated under Quality Audit above, these procedures can be inspected and the firm must certify in writing, if requested, that the firm has complied with this QS/GMP requirement.
The firm must have a written quality plan that defines the relevant design and manufacturing quality practices, resources and activities and how they intend to meet their quality requirements. In addition, written quality system procedures and instructions are required.

6.3 Personnel - 21 CFR 820.25

The firm must document procedures that describe what training programs are necessary to assure personnel and trained to adequately perform their jobs. Look for examples (Device History Records (DHR), in-process failure records, etc.) where personnel failed to perform, or inadequately performed a task; e.g., bonding, molding, assembly. These are indications that training procedures are deficient, or required training has not been provided, or personnel with inadequate education, background, training or experience are performing these duties. Also,

1. Verify the firm has procedures for identifying training needs.

2. Review training records to assure training is documented and being conducted as required by their procedures.

3. Verify all personnel have been made aware of defects and errors that may occur if they fail to properly perform their jobs.

4. Verify personnel involved in verification or validation activities have been made aware of defects and errors that may be encountered as part of their job function.

6.4 Document Controls - 21 CFR 820.40

Manufacturers are required to have written procedures for the approval and distribution of documents. The approval procedures must assure the documents meet the requirements of the QS/GMP as well as assuring they are adequate for their intended use. Obsolete documents must be removed from circulation and documentation of document approval must include a signature and date. Removal (or prevention of use) of obsolete documents must be verified. Verify that written procedures (manufacturing, design, quality control, laboratory, etc.) are signed and dated as approved.

When reviewing Device Master Record (DMR) and DHR documents, assure that those in use have been signed and dated as approved. All documents prepared to comply with the QS/GMP must be available at the point at which they are to be used or otherwise needed. Assure that they are.

Changes to all approved documents must be reviewed and approved, communicated to appropriate personnel in a timely manner and maintained. Review document change records to assure they include a description of the change, identification of the affected documents, an appropriate approval signature, approval date and effective date of the change. Changes should not be implemented prior to approval. The approving official should be the same person or from the same department as the original approver. If not, there must be documentation that specifically designates who is responsible for approving the change.
6.5 **Purchasing Controls - 21 CFR 820.50**

Manufacturers are required to have procedures to ensure all purchased or otherwise received product and services conform to their specified requirements. A lack of adequate control over purchases has resulted in a significant number of recalls due to component failures. FDA is not regulating component suppliers, therefore the purchasing control requirements should provide manufacturers with additional assurance that only acceptable components are used to manufacture finished devices.

1. Verify that the firm's written procedures include requirements, including quality requirements, that suppliers, contractors and consultants must meet.

2. Verify that the firm evaluates and selects potential suppliers, contractors and consultants on the basis of their ability to meet the specified requirements.

3. Verify that the type and extent of control needed over the product, suppliers, services, contractors and consultants has been defined and is based on the evaluation results.

4. Verify that there are records of acceptable suppliers, contractors and consultants.

5. Verify that the firm has written, approved, and specified requirements, including quality requirements, for purchased or otherwise received products and services.

Where possible, the approved purchasing documents should include an agreement that the suppliers, contractors and consultants will notify the manufacturer of any changes in the product or service. Manufacturers must evaluate these changes to determine whether they affect the quality of their finished devices.

Again, as stated previously under Quality Audit above, Investigators are not to review actual results of supplier audits. The procedures for those audits may be reviewed.

6.6 **Identification and Traceability - 21 CFR 820.60**

The manufacturer is required to have written procedures for identifying products during all stages of receipt, production, distribution and installation to prevent mix-ups. The manufacturer has flexibility to identify product by whatever means they describe in their procedure.

Review DHRs against the DMRs to assure the appropriate components were used in each stage of the manufacturing process. Further compare the DHRs against the incoming and in-process acceptance records to assure only acceptable (passed) product was used in each subsequent stage of the manufacturing process.

For certain devices;

a. Intended for surgical implant into the body,

b. or to support or to sustain life,
c. and whose failure when properly used in accordance with labeled instructions for use can be reasonably expected to result in a significant injury to the user, the manufacturer must have written procedures for identifying each unit, lot or batch of finished device or where appropriate components with a control number. The procedures should facilitate taking corrective action, and the identification must be documented in the DHR.

This control number can be the same as the Identification number used to prevent mix-ups during manufacture or may be different. The control number is used for those devices that used to be defined as "critical." However, the list of "critical devices" was last updated in 1988 and there are no plans to update it. Therefore, the definition needs to be used to determine if a manufacturer has any devices that must meet this QS/GMP requirement.

Traceability need only go the level of the initial consignee, which is the first person(s) outside of the manufacturer's control. This control number would be used to facilitate complaint investigations, recalls, market withdrawals, market corrections, etc.

The traceability requirement should not be confused with the tracking regulation under 21 CFR 821. The tracking regulation requires certain devices to be tracked to the end user or patient through the entire distribution process.

Components of a device subject to traceability requirements must be identified with a control number where appropriate. Manufacturers must define which components are to be identified with control numbers and provide justification for those that are not identified with control numbers.

The manufacturer can utilize the definition of critical component in the original GMP regulation as guidance. However, they should perform some sort of risk analysis first on the finished device, and subsequently on the components of that device to make this determination.

Manufacturers must evaluate their device and identify the components that "are essential to the proper functioning of the device" i.e. "critical." When an investigator chooses to challenge a manufacturer's selection or non-selection of a component as "essential to the proper functioning of the device," documentation for CDRH evaluation must be collected to support this challenge.

The QS/GMP requires manufacturers to evaluate their suppliers and to evaluate their quality data for problems. One method of doing this, similar to the requirements in the old GMP, is to record the percentage of "essential" component rejects per lot, as well as the percentage of lots rejected. If the manufacturer has the raw accept/reject data in a form that can be evaluated to determine supplier performance, and is periodically doing this evaluation, this would be acceptable in lieu of recorded percentages.
6.7 Production and Process Controls - 21 CFR 820.70

6.7.1 Production and Process Specifications
Verify specifications and documented work instructions are provided for all processes in which variations could result in failure of the finished device to meet specifications.

Typical process examples are molding, heat treatment, welding, sterilization, blending, package sealing, solvent bonding, etc. Drawings may often be used for assembly, fabrication, etc. and in some cases training and workmanship standards may suffice in lieu of written procedures e.g., hand soldering.

Verify specification and procedure changes, and new specifications and procedures are reviewed and approved using a formal process and procedure. Changes in work instructions, drawings and other instructional procedures should also be made according to formal controls. Approval is often documented by using a standard form such as an Engineering Change Notice (ECN), Drawing Change Request (DCR), or other approval documents.

6.7.2 Reworking
Determine if devices or components are reworked during manufacture. Generally, routine reconditioning or repair prior to distribution is not considered reworking unless the activity would adversely affect the reliability, safety, or effectiveness of the device.

Routine replacement of defective parts would normally not be considered reworking, unless the structure of the supporting materials such as adhesives, epoxies, solders, etc., must be changed or modified. Replacing a defective plug-in circuit board would not normally be considered reworking. Replacement of integrated circuit chips where supporting material must be removed, replaced or modified would be considered reworking. Patching, regrinding, remelting, structure-strengthening, reheating, resterilization, etc., would also be considered reworking. If, in a reconditioning or repair process, the device is modified so that it does not conform to its original specifications, the activity then becomes remanufacturing.

Where reworking is not a routine part of the process, a high reworking rate may indicate production problems such as inadequate training or procedures which should be evaluated and corrected.

Verify written rework procedures are provided for guidance. In cases of routine rework, determine if the manufacturer has assessed the effect of reworking on the finished device or component and if the evaluation is documented.

6.7.3 Buildings
Facilities used for the manufacture, handling and storage of medical devices, components, or in-process material must provide adequate space designed to prevent mixups and to assure orderly handling of:

a. Incoming product (see definition of "product" 21 CFR 820.3(r))
b. Rejected or obsolete product  
c. In-process product  
d. Finished devices  
e. Labeling  
f. Reworked or repaired devices  
g. Equipment  
h. Molds, patterns, tools, records, drawings, blueprints  
i. Testing and laboratory operations  
j. Quarantined products

6.7.4 Environmental Control

Where environmental conditions at the manufacturing site could have an adverse effect on a device's fitness for use, these environmental conditions must be controlled to prevent contamination of the device. In general, this applies to the manufacturing environment and areas used for storage of product and the finished device.

Computers, computer components and software storage media may be sensitive to the environment especially in regards to temperature, humidity, electrostatic discharge (ESD), electromagnetic interference (EMI) and dust/dirt. Other products or finished devices may need to be handled or manufactured in a cleanroom environment to minimize bioburden. Written procedures are needed to assure the environment is controlled as required.

Verify there are documented inspections of these environmental controls that demonstrate the environmental control systems are properly functioning. Review of microbiological test results for air, water and surfaces are indicators on how well the environment is being controlled. Fluctuating results, or periodic spikes may indicate problems.

6.7.5 Contamination Control

There should be written cleaning procedures and schedules adequate to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality.

Verify the washing and toilet facilities for production and laboratory personnel are clean and adequate.

Verify, where special clothing requirements are necessary to ensure a device is fit for its intended use, there are clean dressing rooms provided for personnel.

Verify there are procedures designed to prevent contamination of equipment, components or finished devices by rodenticides, insecticides, fungicides, fumigants, hazardous substances and other cleaning and sanitizing substances, if used. Verify these procedures are adhered to, when they exist.

Verify eating, drinking, and smoking by personnel are limited to designated areas when such activities could have an adverse effect on a device's fitness for use.
Verify all sewage, trash, byproducts, chemical effluent and other refuse is disposed of in a timely, safe and sanitary manner.

### 6.7.6 Personnel

Each manufacturer must have written requirements for health, cleanliness, personnel practices and clothing of personnel if contact between such personnel and the environment could reasonably be expected to have an adverse effect on product quality. The manufacturer must assure maintenance or other temporary personnel required to work in specially controlled environments are properly trained or supervised by a trained individual.

Verify personnel in contact with the subject device or its environment are clean, healthy and suitably dressed per the firm’s requirements. Verify personnel who, by medical examination or supervisory observation, appear to have a condition which could adversely affect the device are excluded from affected operations until their condition is corrected. Verify the firm’s written procedures require personnel to report such conditions to their supervisor.

### 6.7.7 Equipment

Equipment used in the manufacturing process must be appropriately designed, constructed, placed and installed to facilitate maintenance, adjustment and cleaning.

Where maintenance of equipment is necessary to assure manufacturing specifications are met, verify there is a written procedure/schedule for maintenance and written documentation showing the scheduled maintenance activities are performed. Where a piece of equipment has inherent limitations or allowable tolerances, verify they are visibly posted on or near each applicable piece of equipment or is readily available to personnel responsible for performing maintenance on or operating that piece of equipment.

Verify the manufacturer is performing periodic inspections per written procedures to assure they are adhering to their applicable maintenance schedules.

Verify any inherent limitations or allowable tolerances are visibly posted on or near equipment that requires periodic adjustment. If not, they should be readily available to personnel performing these adjustments.

When manufacturing material could reasonably be expected to adversely effect the quality of a product, verify the material is being removed from the product or limited to a specified amount that will not adversely affect the product's fitness for use. Assure this use and removal or limitation is being done in accordance with written procedures. Verify the removal or limitation of the manufacturing material is documented.

When computers or automated data processing systems are used as part of the production or quality system, verify the software has been validated for its intended use according to a written protocol.
Verify changes to this software are validated before approval and issuance. Verify these validation activities are documented. See Process Validation section above.

6.8 Inspection, measuring, and test equipment - 21 CFR 820.72

Manufacturers must assure all inspection, measuring and test equipment (including mechanical, automated or electronic inspection and test equipment) is suitable for its intended use and is capable of producing valid results. This would normally be done through installation, operation and performance qualification of the equipment. Automated equipment must also assure the software has been validated for its intended use. Verify this type of equipment has been routinely checked, calibrated and inspected according to the written procedures and documented as having been done.

Verify there are written procedures for calibration, inspection, checks and maintenance for this type of equipment. Verify that the procedures include provisions for handling, preservation and storage of this type of equipment to assure its accuracy and fitness of use is maintained. Verify these activities are documented.

Verify written calibration procedures include specific directions and limits for accuracy and precision. Review records of calibration records to verify equipment meets the required limits for accuracy and precision. When the limits are not met, there should be written provisions for remedial action to reestablish those limits and to evaluate whether there was any adverse effect on the device's quality. Verify these remedial actions and evaluations are documented.

Verify inspection, measuring and test equipment have calibration standards traceable to a known national or international standard. If national or international standards are not practical or available, the manufacturer must use an independent reproducible standard. If no applicable standard exists, the manufacturer must produce and maintain an in-house standard.

Verify calibration records are displayed on or near each piece of equipment or readily available to personnel using such equipment and responsible for calibrating the equipment and that they include the following:

a. equipment identification
b. calibration dates
c. next calibration date

6.9 Acceptance Activities - 21 CFR 820.80 and 21 CFR 820.86

All manufacturers of medical devices must establish and maintain procedures to verify all products meet specifications. Acceptance activities include, but are not limited to inspection and test, certificates of analysis, and supplier audits.

The firm must define the activities for receiving, in-process, and final acceptance of all parts, components, and materials that will become part of the finished device or part of the manufacturing
process. NOTE: the definition of the word "product" now means components, manufacturing materials, in-process devices, finished devices and returned devices.

Receiving acceptance activities must include procedures for acceptance of incoming product. Firms do not need to inspect each lot, batch or item. However the firm must have a defined method of evaluating whether that lot, batch, or item meets the established specifications. The decision of whether to accept or reject the product must be documented.

In-process acceptance activities may be conducted at appropriate points in the process to ensure in-process specifications have been met. The firm must have written procedures that include, but are not limited to, descriptions of equipment needed, required methods, and acceptance criteria. There must be procedures to ensure in-process product is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals have been received and documented.

Final acceptance activities should be performed for each production run, lot, or batch of finished devices. These activities should include, but are not limited to, descriptions of any equipment required, the methods used to perform the activity, and the acceptance criteria. Finished devices must be controlled until released.

Finished-device acceptance activities must include a review of the DHR to ensure the device was processed and completed per the DMR. The review must be performed by a designated individual. The results, including the individual's signature must be documented.

Acceptance activities must be recorded. The records must include the activities and dates performed, the results, the signature of the individual(s) conducting the activities, and the equipment used, if appropriate.

6.10 Labeling and Packaging Control - 21 CFR 820.120 and 21 CFR 820.130

Verify the manufacturer has procedures to control labeling operations. The procedures should assure the following:

a. Labels are printed and applied so as to remain legible and affixed during the customary conditions of processing, storage, handling distribution and where appropriate, use.

b. Labels are not released for storage or use until examined by a designated individual(s) for accuracy, including (where applicable):

   1. correct expiration date
   2. correct control number
   3. storage instructions
   4. handling instructions
5. any additional processing instructions

c. The release of labels is documented in the DHR by date of release and signature of person performing the examination.

d. Labels are stored in a manner that provides proper identification and is designed to prevent mixups.

e. Labeling and packaging operations are controlled to prevent labeling mixups.

f. The label and labeling used for each production unit, lot or batch is documented in the DHR.

g. Where a control number is required by 21 CFR 820.65, that control number is on or accompanies the device through distribution.

Verify the firm's packaging and shipping containers are designed and constructed to protect the device from alteration or damage during its customary conditions of processing, handling, storage and distribution. For devices labeled as sterile, this data will normally be found with the firm's sterilization validation data. Complaints and returns are places to look to see if the packaging and shipping containers do not provide this type of protection.


The firm should have written procedures in place that will ensure mixups, damage, deterioration, contamination or other adverse effects do not occur to product during handling and storage. Examples: ESD controls may be needed in areas where products with sensitive circuitry are packaged and stored. Segregated warehouse areas by physical or computerized means may be employed to prevent mixups relative to quarantined and released product or between similarly packaged products. Other warehouse practices should also be evaluated. Warehouse cleanliness is important for products with minimal packaging that are meant to be kept clean.

The procedures should assure no obsolete, rejected, or deteriorated product is used or distributed. There should also be procedures that describe how product will be authorized as received from and dispatched to storage areas and stock rooms. A review of distribution records cross-referenced to final inspection and release records and quarantine records should be done to verify obsolete, rejected, or deteriorated product has not been used or distributed. Records of receipt and dispatch should be reviewed to assure procedures are being followed.

When the quality of product is known to deteriorate over time, it must be stored in a manner that facilitates proper stock rotation. Its condition must be assessed as appropriate. Additionally, where a device's fitness for use or quality deteriorates over time, written procedures must ensure expired or deteriorated devices are not distributed. For raw materials or in-process materials, this may mean periodically performing incoming or in-process inspection and test. For finished devices with expiration dates, this may require the performance of shelf-life stability studies.
Written procedures are required to ensure only devices approved for release are distributed. The procedures must also ensure purchase orders are reviewed for ambiguities and errors and that any found are resolved before devices are released for distribution.

Distribution records are required and they must contain, or make reference to the location of:

   a. Name and address of initial consignee
   b. Identification and quantity of devices shipped
   c. Date shipped
   d. Any control number(s) used.

When devices require installation, there must be written procedures that describe the installation and inspection instructions, and where appropriate, test procedures. The installation instructions must be sufficient to ensure proper installation so that the device will perform as intended after installation. Service records can be reviewed to verify extra service calls are not required immediately after installation to make the device perform as intended. Installation instructions must be provided with the device or made available to the personnel responsible for installing the device.

The personnel installing the device must document the inspection and any test results that demonstrate proper installation. They are responsible for ensuring the device is properly installed, inspected and tested (when required) in accordance with the manufacturer’s instructions and procedures.

**6.12 Records - 21 CFR 820.180, 820.181, 820.184, 820.186**

All of the records required by the QS/GMP are to be maintained at the manufacturing facility or other location that is reasonably accessible to responsible officials of the manufacturer and employees of FDA designated to perform inspections. These records are to be made readily available for review and copying by FDA employees. These records must be legible, and stored in a manner that minimizes deterioration and loss. Automated record or document management systems shall be backed up.

The firm should be encouraged to mark records they feel are confidential to assist FDA in determining what information may be disclosed under the Freedom of Information Act (FOIA). Impress upon manufacturers that marking all copies of records and documents confidential does not aid FDA in making its FOIA determination.

Records required by the QS/GMP must be retained by the manufacturer 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. This does not mean that stability data is needed for all devices to determine "expected life of the device." Manufacturers may use service records, marketing analyses or other methods to determine this expected lifetime. Stability studies are only needed to support labeled expiration dates.

21 CFR 820.180 General Requirements for Subpart M-Records does not pertain to the reports required by 21 CFR 820.20(c) Management review; 820.22 Quality audits; and supplier audit reports under
820.50(a) Evaluation of suppliers, contractors and consultants. It does apply to the procedures required under those sections.

**6.12.1 Device master record (DMR)**

A device master record may exist in many forms. For example:

- one or more files or volumes, or
- a list referring to the location of all documentation required by the master record, reflecting the latest revisions, and signed and dated as having been checked for accuracy and approved, or;
- any combination thereof.

Ensure all the following documentation required by the QS/GMP is included or referenced in the device master record and that there is a formal method for approving and making changes to this documentation, including procedures:

- device specifications (e.g. drawings, composition, formulation, component specifications, and software specifications)
- production process specifications (e.g. equipment specifications, production methods, production procedures, and production environment specifications)
- quality assurance procedures and specifications (e.g. acceptance and reject criteria, test methods, and quality assurance equipment to be used)
- packaging and labeling specifications (e.g. labels and packaging to be used, and methods and processes to be used)
- installation, maintenance, and servicing procedures and methods

**6.12.2 Device history record (DHR)**

Verify history records representing individual devices or lots of devices exist for all finished devices manufactured. The history record should reflect that all operations, processes, etc., described in the master record have been accomplished. In addition, the history record is specifically required to contain, or refer to the location of, the following information:

- date(s) of manufacturing,
- quantity manufactured,
- quantity released for distribution,
- any device identification(s) and control number(s) used,
e. the primary identification label and labeling used for each production unit, and,

f. the acceptance records which demonstrate the device is manufactured in accordance with the DMR.

The QS/GMP does not require control numbers or traceability for all devices. Control numbers/traceability are, however, required for in vitro diagnostics (IVD's) subject to the labeling requirements of 21 CFR 809.10 and devices subject to the Radiation Control for Health and Safety Act. The QS/GMP does require control numbers/traceability for high risk (previously described as critical) devices. Verify history records contain evidence that labeling was examined prior to actual use.

The GMP does not require device history records be maintained at one location. For example, the history record for an operation may be maintained at that operation location in logbook form. However, history records should be maintained in a form where they can be readily reviewed and signed prior to device distribution as required by 21 CFR 820.80.

6.12.3 Quality System Record (QSR)

The QSR must include, or make reference to the location of, the procedures and documentation required by the QS/GMP that are not specific to a particular type of device. This includes all procedures and records required by 21 CFR 820.20, Management Responsibility. It may also include general procedures for complaint handling, cleaning, maintenance, etc. The QSR should be prepared and approved as required by 21 CFR 820.40, Document Controls.

It is not important in which record, DMR or QSR, a particular procedure or document is included. It is more important that the manufacture have the procedure or document and that it is readily available for our review.
7 PRE-APPROVAL DEVICE INSPECTION (PMA, AND CLASS III 510(k))

Pre-Approval inspections are confined to PMA and Class III 510(k) devices. The purpose of these inspections is two-fold:

a. Verify that the information submitted with the particular 510(k) or PMA in regard to manufacturing is accurate. (i.e. Does the firm have the equipment, personnel, facility, etc. to manufacture the device under review? Are they complying with the product or process specifications listed in their application?)

b. Assess the firm’s ability to meet the Quality System/GMP Regulation.

If any changes to the application have occurred, it should be determined whether these changes have been adequately communicated to the appropriate reviewing staff in CDRH/Office of Device Evaluation.

See Compliance Program 7383.001 for further instructions on doing device pre-approval inspections.


8  STERILE DEVICES

If the firm is manufacturing sterile devices, CP 7382.830A, Attachment A, must be followed.

There should be records to show how the sterilization process was validated. ANSI/AAMI/ISO Standards are published for the major sterilization processes and can be used for guidance in the evaluation of the process validation. If a firm applies the ANSI/AAMI/ISO standards appropriately and follows them in validating a sterilization process, CDRH will be satisfied with the approach. However, a firm is NOT required to follow these standards. They may choose to validate their sterilization process using some other method. If they do, they will need to explain the scientific validity of the method they used. Obtain appropriate records to document any deficiencies related to validation.

A determination should be made as to whether the firm is or may be producing nonsterile devices. There are several ways of making this determination:

a. Review lot release records and sterilization process records that show what the cycle parameters or absorbed dose were for each of the lots released. Compare those parameters to the validated cycle parameters. All of the released lots should have met the validated cycle parameters. If any lot did not meet the validated cycle parameters an investigation should have been made. If any of the nonconforming lots were released, they may be non-sterile.

b. Review the firm's bioburden data to identify the type and resistance of the bioburden on the device. If the cycle used is bioburden based then the cycle must be able to demonstrate that the appropriate sterility assurance level (SAL) has been obtained prior to release of the sterilized lot. Be aware of seasonal fluctuations in the type and amount of bioburden which can be found on the devices before sterilization.

c. Review the firm's current product and packaging to determine if it is the same as that used for the validation of the sterilization process. Changes in the packaging materials need to be evaluated and may require revalidation.

The SAL is the probability of a unit being nonsterile after exposure to a valid sterilization process. The SAL varies according to the intended use of the device. Sterilized articles not intended to contact compromised tissues are generally thought to be safe for use with an SAL of 10^-3; that is, a probability of one nonsterile unit in a thousand. Invasive and implantable devices should have an SAL of 10^-6; that is, no more than one nonsterile unit in a million. In practice, many firms use overkill cycles which assure an even lower probability that a device will be nonsterile.

Review the firm's investigation reports for any lots that had positive sterility test results and/or positive biological indicator (BI) results.

Review the firm's records to determine if any reworking (resterilization) procedures were performed due to process failure.
The firm’s validation reports should include adequate data to assure device performance and package seals were not adversely affected by any reworking.

Test methods in use should be based on accepted test methodologies. The tests should be performed properly so as to be able to detect positive sterility/BI test results. If an in-house test method is used, it should have been validated to show it is as capable of detecting nonsterile units as readily as referenced methodologies.

If reworking (re-sterilization) was performed, it should be documented and be permitted per the firm’s validation data. Verify the resterilized lots were adequately reworked, and were properly tested prior to release. The firm should have conducted a failure investigation prior to release to determine why the initial test results were positive.
9 THE SMALL MANUFACTURER

There is no official definition of a small manufacturer, although 10 or fewer employees is often used as the rule of thumb. An investigator should realize that a small firm usually does not need the same degree of documentation necessary as required for a large firm to achieve a state of control. Many of the written procedures required by the Quality System/Good Manufacturing Practices may be more brief and less detailed for a small manufacturer or a manufacturer of less complicated devices, unless the firm is producing nonconforming devices. Evidence that the firm is producing nonconforming devices may indicate the need for more detailed procedures.

At a minimum, the small manufacturer must have the following:

a. Adequate space for components, finished devices, and manufacturing processes
b. A DMR containing the production and device specifications
c. Testing/release according to specifications
d. A DHR containing the test results
e. Training/qualifications of employees
f. Audit procedures

An investigator who understands the purpose and meaning of the various QS/GMP requirements will not merely follow the words verbatim, but will apply the requirements properly to any operation which applies to the device manufacturing firm. If the guidance in the book entitled "The FDA and Worldwide Quality System Requirements Guidebook for Medical Devices" is followed, an investigator can apply them to any situation, regardless of the size of the firm or the complexity of its operations.
10 WRITTEN PROCEDURES - "ESTABLISH"

The new Quality System/GMP Regulation has numerous references to establish and maintain certain procedures. Establish is defined as define, document and implement (do).

The purpose of written procedures is to provide instruction and guidance, to assure uniformity and completeness, and for communicating and managing operations.

In large manufacturing operations involving many unskilled people and multiple operations, detailed written procedures are usually necessary. In a small firm, communication lines are usually short, fewer people are involved, and management is readily available to provide guidance so that the length and depth of written procedures is usually less.

Often, training and work experience are valid substitutes for detailed 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 investigator must evaluate each situation and determine the need for a detailed written procedure on the basis of training and the knowledge possessed by the operator and the control needed. Typically, a detailed written procedure may not be necessary when:

a. The activity is very simple.

b. Straight forward quantitative rather than qualitative standards determine acceptability.

c. The operation is performed by skilled personnel.

In a small firm, the investigator may conclude that the Quality System/GMP Regulation for a written procedure is not needed, except where appropriate. Such a decision, however, must be supported by observation that sufficient control is present to meet the intent of the written procedure, and the fact that nonconforming devices are not being produced.

When the Quality System/GMP Regulation requires a procedure, all appropriate procedures shall be "written." If the manufacturer does not have the applicable procedure, the investigator must evaluate the controls in place and determine if they are adequate without written procedures. Such decisions can be made taking into consideration such factors as the number of mistakes, rework, rejects, complaints, etc., that can be related to the operation for which the procedures are intended.

Every time the QS/GMP requires a written procedure, it does NOT mean a separate, discrete procedure. Many of the required written procedures can be combined and written up as system procedures or procedures that cover several areas, i.e. "packaging, distribution, installation."

An investigator should not insist that a manufacturer meet a QS/GMP requirement that does not contribute to assuring conformance to specifications simply because it is part of the new regulation. Section 519(a)(4) of the FD&C Act prohibits record keeping requirements that are unduly burdensome to a device manufacturer.
ATTACHMENTS

ATTACHMENT A-MEDICAL DEVICE INDUSTRY INITIATIVE

The following guidance/procedures should be followed.

Background

In 1996, FDA initiated a pilot program involving the medical device industry to enhance FDA/industry communication, optimize resource utilization, and provide firms with prompt closure to corrected inspectional observations and nonviolative inspections. The pilot program, now known as the Medical Device Industry Initiatives program (MDII), includes eligibility criteria and procedures for preannounced inspections, the annotation of items on form FDA-483, Inspectional Observations, with promised or completed corrections and postinspectional notification to establishments regarding their compliance status.

The MDII program is currently restricted to inspections of medical device firms that manufacture only medical device products, and not to those who manufacture products that may cross different program areas like devices/drugs.

FDA currently maintains contracts with the States of California, Colorado, and Texas to conduct medical device inspections on behalf of FDA. This program will include those inspections done under State contract for FDA.

This program will not impact on violative situations because there will not be a decreased level of enforcement, if enforcement is necessary. Previous FDA experience indicates that the overall out-of-compliance rate for preannounced foreign inspections is comparable or even greater than the overall out-of-compliance rate for domestic inspections where preannouncements were not generally made prior to implementation of the MDII program.

I. Preannounced Inspections

A. Basic Premise

1. This program is intended to be applied only to those medical device manufacturers that meet the criteria for consideration.

2. The eligibility of an individual firm for participation in this program is at the discretion of the district office using clearly described criteria. (See section I.B. of this document).

3. The implementation of this preannounced inspection program is intended to be flexible, based on appropriate considerations of the agency and firm.

4. The preannouncement should generally be no less than 5 calendar days in advance of the inspection. Should a postponement be necessary, the decision as to the time of
rescheduling rests with the investigator/team, but the new inspection date should not exceed 5 calendar days from the originally set date. Inspections may be conducted sooner than 5 calendar days if requested by the firm and if this date is acceptable to the investigator/team.

5. To participate in this program, firms are expected to meet the commitment to have appropriate records and personnel available during the inspection.

6. Preannounced inspections will not limit an investigator’s authority to conduct the inspection. Inspections will be as in depth as necessary.

B. Criteria for Consideration

The criteria to be used by the district office to determine whether it is appropriate to preannounce a planned inspection will include:

1. Type of Inspection:
   a. Premarket inspections (PMA and 510(k)),
   b. Foreign inspections,
   c. Quality System/Good Manufacturing Practice (QS/GMP) inspections of medical device establishments:
      • Biannual routine inspections,
      • Initial inspections of newly registered establishments,
      • Initial inspections of new facilities,
      • Initial inspections under new management and/or ownership.
   d. Non QS/GMP inspections other than:
      • Immediate and urgent responses to complaints,
      • Immediate and urgent follow-up to informant information, and
      • Immediate hazard to health recall follow-up inspections.
   e. e. Recall follow-up inspections at medical device manufacturers/ initial importers (under new regulations, the U.S. designated agent).
      (Bioresearch monitoring (BIMO) inspections are done per Compliance Programs 7348.808, 7348.808A, 7348.809, 7348.810 and 7384.811. Procedures described in those programs for preannouncements will be followed).

2. Eligibility Criteria:
a. QS/GMP inspections of firms with nonviolative histories (inspections classified as no action indicated (NAI) or voluntary action indicated (VAI)). For VAI, adequate corrections of conditions observed and listed on FDA-483 during the previous inspection were verified and did not lead to any further agency action.

b. To remain eligible for preannounced inspections, firms must have a history of having individuals and/or documents identified in previous preannounced inspections reasonably available at the time of the inspection.

C. Procedures

1. The investigator designated to conduct the inspection will contact or, if unavailable at the time of the call, leave word for the most responsible individual at the facility.

2. Changes in dates should be kept to a minimum. If a change is made, a new date should be provided as soon as possible that will facilitate the inspection and accommodate the investigator's schedule.

3. Preannouncements are normally limited to the investigator (or lead investigator for a team inspection) informing the firm of an upcoming inspection. Usually it is appropriate to inform the firm as to the purpose, estimated duration, and the number of agency personnel expected to take part in the inspection. The products or processes to be covered should also be described if this will facilitate and be consistent with the objectives of the inspection.

4. When known, specific records/personnel will be requested at the time the inspection is scheduled.

II. FDA-483 Annotations

A. Basic Premise

1. For all medical device establishments, the investigator will annotate the FDA-483 at the time of issuance to acknowledge an establishment's promised or completed corrective action. Industry should review the annotations on this issued FDA-483 to ensure that there are no misunderstandings on promised corrective actions. (BIMO inspections are excepted from the annotations portion of this program.)

2. A reportable item will not be deleted from FDA-483 because the establishment has promised or completed a corrective action. The investigator will continue to have the latitude to delete the observation if the establishment's response to the observation clearly shows that the observation is in error or to clarify the observation based on additional information provided.

3. FDA investigators will continue to report only significant observations on FDA-483 and to discuss these and other less significant observations with the establishment's management.
B. Procedures

1. Investigators and analysts will discuss all observations with the management of the establishment as they are observed, or on a daily basis, to minimize surprises, errors, and misunderstandings when FDA-483 is issued. This discussion will include those observations that are potentially written FDA-483 items or oral observations. Industry should use this opportunity to ask questions about the observations, request clarification, and inform the inspection team what corrections have been or will be made as soon as possible during the inspection process. Investigators are encouraged to verify the establishment's completed corrective action as long as the verification does not unreasonably extend the duration of the inspection.

2. Where practical, FDA-483 observations should include the number of records of a given type examined, for example, "Two out of 50 records examined were **.*"

3. If the establishment has promised and/or completed a corrective action to an FDA-483 observation prior to the completion of the inspection, all copies of FDA-483 should be annotated (either following each observation or at the end of FDA-483) with one or more of the following comments, as appropriate:

   - Item # XXXX reported corrected but not verified.
   - Item # XXXX corrected and verified.
   - Correction of items XXXX, XXXX and XXXX promised by 00/00/96.
   - Item #XXXX, no comment at this time.

4. If an observation made during a prior inspection is noted as not being corrected or is a reoccurring observation, it is appropriate to note this on the FDA-483.

5. All corrective action taken by the establishment and verified by FDA should be discussed in detail in the establishment inspection report and reported using the Corrective Action Reporting Systems (CARS).

III. Postinspecational Notification

A. Basic Premise

1. As part of this program FDA will issue additional postinspecational notification to establishments regarding their compliance status within 30-45 days of the inspection.

2. The two categories under which firms will receive postinspection notification are:

   a. NAI situations where no FDA-483 was issued or only limited, less significant violations were reported.
b. VAI situations where an FDA-483 was issued but all profile classes were found acceptable. In this circumstance, no regulatory action is contemplated based on the inspection.

3. The postinspctional notification letters that are issued under this program will be mailed under the signature of the district director, in that district in which the establishment is located. For international inspections, they will be issued under the signature of the Director, Division of Program Operations, CDRH.

4. For those inspectional follow-ups where regulatory action is being considered, FDA's existing modes of notification will continue to be used. (BIMO postinspectional correspondence will be issued as appropriate by CDRH/Office of Compliance, Division of Bioresearch Monitoring.)

**Sample Letter: NAI/No 483**

[The following is an example of a letter intended to be issued in situations classified as NAI where no FDA-483 was issued, or only limited less significant violations were reported:]

Date:  
Name:  
Address:  

Dear:  

The Food and Drug Administration (FDA) conducted an inspection of your firm's (description) facility at (address) on (date). The inspection covered the products described below. (list of products and their profile classes)

The areas inspected appear to be in substantial compliance with the applicable requirements of the Federal Food, Drug, and Cosmetic Act and implementing regulations.

Based on these findings, the agency is prepared to endorse applicable pending premarket (PMA) submissions or export certificates for products manufactured at your facility that were specifically inspected. This information is available to Federal agencies when they consider awarding contracts. There may be other products and operations of your firm for which the conclusions from this inspection are not applicable. The agency may separately inspect your firm's facilities to address quality system/good manufacturing practices (QS/GMP's) in these areas.

Your firm has an ongoing responsibility to conduct internal self-audits, to ensure you are continuing to maintain conformance with QS/GMP's. For further information, please contact the following individual at this office: (name and telephone number)
Sample Letter: NAI/And 483

[The following is an example of a letter intended to be used in situations classified as VAI where an FDA-483 was issued, but all profile classes were found to be acceptable. This type of letter should be issued only when no regulatory action is contemplated, including issuing a warning letter:]

Date:
Name:
Address:

Dear:

The Food and Drug Administration (FDA) conducted an inspection of your firm's (description) facility at (address) on (date). The inspection covered the products described below.
(list of products and their profile classes)

While some adverse practices/conditions were observed during the inspection, they do not appear to warrant consideration of regulatory follow-up at this time. These problems were reported to you on an FDA-483 (copy enclosed) issued at the conclusion of the inspection. The problems should be corrected and we encourage you to advise us as to your follow-up actions.

Based on these findings, the agency is prepared to endorse applicable pending premarket (PMA) submissions or Export Certificates for products manufactured at your facility that were specifically inspected. This information is available to Federal agencies when they consider awarding contracts. There may be other products and operations of your firm for which the conclusions from this inspection are not applicable. The agency may separately inspect your firm's facilities to address quality system/good manufacturing practices (QS/GMP's) in these areas.

Your firm has an ongoing responsibility to conduct internal self-audits, to ensure you are continuing to maintain conformance with QS/GMP's.

For further information, please contact the following individual at this office:
(name and telephone number)

Sincerely,

Enclosures: FDA-483
ATTACHMENT B - Temporary Enforcement Moratorium

Date: June 6, 1997
From: Director, Office of Regional Operations (HFC-100)
Director, Office of Enforcement (HFC-200)
Subj: Temporary Enforcement Moratorium - Certain Medical Device GMP violations

To: Regional Food and Drug Directors
District Directors
Investigations Branch Directors
Compliance Branch Directors

The purpose of this memorandum is to establish agency policy, and to describe the rationale for a temporary moratorium on enforcement activities related to validation of changes to medical devices (including changes to device software, such as blood establishment software).

Background
The final rule for the new medical device Quality System (GMP) regulation was published in the Federal Register on October 7, 1996. There are several new features in this regulation, the most important of which are new requirements for medical device design controls. All aspects of the new regulation become effective on June 1, 1997. However, FDA has agreed that for one year (June 1, 1997 - May 30, 1998), we will not pursue enforcement actions, issue Warning Letters, or cite FDA 483 observations related to violations of design control requirements. It is very important that all FDA personnel understand and adhere to this temporary moratorium regarding design controls.

Current GMP Enforcement
Under the existing device GMP regulations, changes made to a device (including changes to device software) are considered to be specification changes, and must be documented, validated and approved, as required by 21 CFR 820.100(a)(2). In the past, investigators have correctly cited inspectional observations on the FDA 483 for failure to validate such device changes (including software changes).

Design Controls and Device Software
Device software development is primarily a design process, and will be regulated in the future under the design control provisions of the new device Quality System regulation. Beginning on June 1, 1997, all current device GMP requirements regarding validation and approval of device changes (including software changes) will be moved to 21 CFR 820.30, Design Controls. For the one year period until June 1, 1998, an investigator's observations regarding design controls will be identified on a separate Design Control Inspectional Strategy (DCIS) Report (copy attached) to be provided to the manufacturer at the end of the inspection. However, design control observations will not be included on any FDA 483, and FDA will not pursue regulatory actions for design control violations. This includes all aspects of
documentation, approval and validation of changes for any device design, and specifically includes validation of device software changes. It also includes software changes and software validation by blood establishment software manufacturers. This temporary relaxation of current regulatory requirements was the subject of a joint teleconference on October 3, 1996, involving CDRH, CBER, and ORA field and headquarters, and has the concurrence of all three Agency components.

Validation of Quality Systems Software

The current device GMP (21 CFR 820.61) requires validation of all software used to automate quality assurance and device manufacturing operations. Beginning on June 1, 1997, this software validation requirement is moved to section 820.70(i) and is expanded to include software used to implement any aspect of the quality system. This will include design software such as computer-aided design (CAD), computer-aided software engineering (CASE) and computer-controlled analytical equipment used by research and development for device design activities. There is no moratorium on enforcement of this requirement, but investigators should be careful in their interpretation and observations, especially during the first year of implementation. Comment #136 in the preamble to the new Quality System regulation (copy attached) provides guidance for interpretation and implementation of this software validation requirement for quality systems software. Additional software validation guidance from CDRH is under development.

For some quality systems software that is directly interfaced with device software (e.g., automated testing equipment), it may be difficult to separate out quality system versus device functionality. In such cases, inspectional observations should appear on the DCIS report rather than the FDA 483.

Other Quality System Requirements

All other provisions of the new Quality System regulation, (e.g., Purchasing Controls, Nonconforming Product, Corrective and Preventive Action, etc.) are fully enforceable on June 1, 1997. Note, however, that the existing device GMP does not exist on or after June 1, 1997. In many cases, the new Quality System regulation allows more flexibility for the device manufacturer than does the existing device GMP. Therefore, care should be exercised in interpreting the new regulation, and the specifics of its application.

Contacts

Additional guidance will be included in appropriate compliance programs when they issue. If you have further questions regarding these issues, contact Denise Dion, ORA at (301) 827-5645; Stewart Crumpler, CDRH at (301) 594-4659; or Alice Godziemski, CBER at (301) 594-1191.

/s/ /s/
Gerald E. Vince Daniel L. Michels
ATTACHMENT C - FOI and Design Controls

Date: June 3, 1997
From: Director, Division of Compliance Policy (HFC-230) Office of Enforcement
Subj: FOI and the New Device CGMP
To: All District Directors

The new medical device Current Good Manufacturing Practice (CGMP) final rule, also known as the Quality System Regulation, was published in the Federal Register on October 7, 1996 (61 FR 52602). This regulation, which became effective on June 1, 1997, includes design control provisions (21 CFR 820.30) for the first time. As a result of these new regulatory requirements, design control deficiencies and information will be noted on the Design Control Inspectional Strategy Report (June 1, 1997 through May 31, 1998) or on the list of Inspectional Observations (FDA 483) after May 31, 1998. (For additional information, please refer to page number 52604 of the preamble in the October 7, 1996 Federal Register.) Additionally, the design control deficiencies and information will also be discussed in the Establishment Inspection Report.

The design control deviations and information will be related to: (1) the design or development of new devices that have not yet been commercially distributed; (2) devices that are in commercial distribution and are undergoing a design change; or (3) commercially marketed devices which were in the design or development process on or after June 1, 1997, but which have not yet undergone a design change. Some information related to design controls might be the type of information that is considered either: (1) a trade secret, or (2) commercial or financial information that is privileged or confidential as defined in 21 CFR 20.61. If it is, that particular design control information is exempt from public disclosure under the Freedom of Information (FOI) Act. For new devices that have not been distributed, some examples of design control information that should be purged from the documents because it is not publicly known, pursuant to 21 CFR 20.61, are brand and generic names, actual or proposed design, labeling, and specifications.

In view of the above discussion, all field employees who release Agency documents under FOI should be especially careful and diligent in deleting all non-disclosable information. Please forward a copy of this memorandum to all FOI personnel within your district.

If you have any questions, please contact Jeffrey Governale of my staff via electronic mail, facsimile (301-827-0482) or telephone (301-827-0411).

/s/
David K. Haggard