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Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, House of Representatives

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MEDICAL TECHNOLOGY

Quality Assurance Needs Stronger Management Emphasis and Higher Priority

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GAO

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Program Evaluation and
Methodology Division

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The Honorable John D. Dingell
Chairman, Subcommittee on Oversight
and Investigations
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

At your request, we examined FDA's regulation of good manufacturing practices (GMPs) for medical devices. This report presents our findings. We examined the scope of the current and the proposed GMP requirements, implementation of the current regulation, and industry compliance. In this study, we conducted a national survey of FDA's GMP compliance inspectors concerning their credentials and their views on how the GMP program may be improved. We also compared GMP requirements to generally accepted quality assurance standards; extensively analyzed FDA program data; and examined GMP inspection results, compliance enforcement actions, and industry compliance in recent years.

As we have arranged with your office, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from its date of issue. At that time, we will send copies of the report to the Commissioner of the Food and Drug Administration and make copies available to others upon request.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Kwai-Cheung Chan, Director of Program Evaluation for Physical Systems Areas, at (202) 275-3092. Other major contributors to this report are listed in appendix VIII.

Sincerely yours,

Eleanor Chelimsky
Assistant Comptroller General

Executive Summary

Purpose

Good manufacturing practices are quality assurance procedures contained in the 1978 Good Manufacturing Practices (GMP) regulation, whose intent is to help prevent the production and distribution of unsafe or ineffective medical devices. In spite of the regulation, some critical and life-supporting devices such as emergency ventilators and heart valves have been recalled from the market recently because of manufacturing-related defects.

The House Subcommittee on Oversight and Investigations asked GAO to describe and analyze the Food and Drug Administration's (FDA) GMP compliance program. With the concurrence of the Subcommittee staff, GAO pursued two study objectives: (1) to develop an analytical description of the program that the Food and Drug Administration has established to define and enforce quality assurance in device manufacturing, and (2) to provide a qualitative and statistical review of FDA's inspection and compliance actions.

Background

FDA employs three principal programs to regulate the safety and effectiveness of medical devices: (1) premarket review, (2) GMPs, and (3) postmarketing surveillance. All three programs were created under authority granted by the Federal Food, Drug, and Cosmetic Act of 1938, as amended by the Medical Device Amendments of 1976. However, because FDA has not fully implemented the 1976 statutory provisions for premarket review, the agency's main source of information to assess the safety and effectiveness of devices before they reach users is the GMP inspection process.

Results in Brief

FDA does not meet its minimum statutory obligation to inspect manufacturers of medium- and high-risk devices at least once every 2 years. Based upon FDA's lowest estimate for the inventory of domestic device manufacturers, over 40 percent were not inspected in fiscal years 1989 and 1990. The frequency of inspections has also been declining, with less than 25 percent of the inventory inspected last year. Foreign manufacturers must also be inspected by FDA, but they have been inspected only about once every 8 years.

Furthermore, domestic inspections are generally not coordinated with market introduction, the time when product design and manufacturing problems are most likely to appear. As a result, during fiscal years 1987-90, 33 percent of domestic manufacturers with recalled devices had not received a GMP inspection within the 2 years before their products were

recalled. These recalls involved defects, caused by either design or manufacturing problems, that posed the threat of serious injury or death. When inspections had occurred within 2 years before the manufacturing-related recalls, 73 percent did not find serious GMP violations. The failure to identify quality assurance problems that were subsequently associated with a product recall is partially attributable to FDA's policy limiting device-specific technical training for GMP inspectors.

Gaps in FDA data preclude an overall assessment of the GMP program; however, recent reported data show that the device industry has not lowered its rate of serious GMP violations as it gained experience with the GMP regulation; instead, these violations have tended to persist over time; and device recalls have not motivated the manufacturers involved to substantially reduce their rate of serious GMP violations found on subsequent inspections. Their rate remained higher than the industry average.

Principal Findings

GMP Requirements

GMP requirements are defined in the 1978 GMP regulation in terms of quality assurance objectives that apply to all medical devices. During the last 12 years, FDA has changed its interpretation of these objectives, shifting to more stringent requirements, and the agency has recently tightened its requirements for the process of device design. Although these stronger requirements are consistent with international quality assurance principles, they are not self-explanatory and their application requires FDA inspectors to have extensive knowledge of device technology. The new requirements could also improve the efficacy of the GMP regulation. Determining if they do will require an empirically valid study that collects data on both preimplementation and postimplementation measures.

Inspection Organization

Until 1990, the effectiveness of GMP inspections was limited by a lack of coordination with market introduction. GMP inspections are now part of the approval process for the small percentage of high-risk devices that must be approved by FDA before marketing. Additionally, a pilot premarket review program was recently started for another small group of high-risk devices, which may also result in a premarket GMP inspection of the device manufacturer. However, unlike the premarket approval process, the pilot review program does not transmit technical data to field offices and

inspectors, to help them target inspections to the riskiest changes in technology.

Inspector Qualifications

FDA's shift to more stringent GMP requirements gives FDA inspectors greater authority and responsibility to assess technical dimensions of device specifications and manufacturing processes. However, current classroom training and job assignment policies severely limit inspectors' knowledge of device technology and ability to identify quality assurance problems in complex devices and manufacturing processes.

Missing Data on GMP Inspections and Compliance Enforcement

GAO found numerous cases where serious violations of the regulation or of compliance enforcement actions were not reported by district offices to central FDA files. In addition, district reporting of inspections failed to include important data needed to assess their effectiveness and to assess broad patterns of device defects across manufacturers of the same device. GAO found that these missing data restrict the agency's ability to monitor manufacturing problems nationally and to assess whether appropriate compliance actions have been taken.

GAO also found two additional gaps in FDA data. First, FDA has conflicting estimates for the inventory of domestic manufacturers of medium- and high-risk devices. Consequently, some manufacturers may not get inspected because they have not been identified. Second, FDA does not attempt to estimate the inventory of medical devices. Without even an approximate idea of these inventories and how they expand over time, relative to the number of defective devices reaching the market, it is difficult to make an overall assessment of how well the GMP program is working.

GAO believes that district reporting and data system problems may be addressed by the new Field Information System that FDA is currently developing and deploying.

Recommendations

GAO recommends that the Commissioner of FDA:

1. Evaluate the adequacy of its inspection force in light of FDA's failure to meet its statutory inspections obligations and the increasing technical competence needed to conduct device inspections and develop a comprehensive plan to provide adequate technical resources;

2. Meet the statutory obligation for inspecting manufacturers of medium- and high-risk devices;

3. Expand the current pilot program for premarket GMP review of a small group of high-risk devices to include all high-risk medical devices;

4. Complete the development and deployment of the new Field Information System in order to achieve comprehensive district reporting of inspection results and compliance actions;

5. Upgrade documentation of the inventory of device manufacturers subject to GMP inspections and develop an inventory of medical devices to serve as benchmarks to assess GMP program effectiveness and the rate of defective devices over time; and

6. Assess the impact of proposed new GMP regulations by monitoring the inspection process and the rate of defective devices before and after implementation.

Agency Comments

HHS generally concurred with GAO's recommendations; however, the agency raised concerns about inadequate resources. GAO believes that making inspections coincide with the market introduction of new devices should be a top priority even with resource constraints. Indeed, such coordination is not resource-dependent. Likewise, resource constraints should not delay implementation of the three GAO recommendations concerning improved program monitoring and evaluation. These proposed actions are needed to improve the GMP compliance program and to demonstrate that, even with limited resources, FDA is doing all that can be done to ensure the safety of medical devices.

In addition to comments on GAO's recommendations, HHS strongly defended its current "generalist first" policy that limits the technical training available to device GMP inspectors. HHS agreed that improved training would make device inspections more effective and toward this goal has recently initiated a variety of new classroom courses. However, GAO continues to believe that the current inspector assignment policy is inconsistent with a goal of developing the necessary technical skills.

HHS also offered several comments of a technical or editorial nature. In response, GAO made adjustments to the report as appropriate.

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Related GAO Products

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Abbreviations

CAT	Computerized axial tomography
CDRH	Center for Devices and Radiological Health
EC	European Community
EIR	Establishment Inspection Report
FDA	Food and Drug Administration
FIS	Field Information System
GAO	General Accounting Office
GMP	Good manufacturing practice
HIV	Human immunodeficiency virus
HHS	Department of Health and Human Services
ISO	International Standards Organization
NAFL	Notice of Adverse Findings Letter
NAI	No action indicated
OAI	Official action indicated
PQA	Preproduction quality assurance
RACS	Regulatory Action Control System
VAI	Voluntary action indicated

Introduction

Background

The Food and Drug Administration (FDA)—which regulates medical devices during all phases of their development, testing, production, labeling, and distribution—recognizes more than 4,000 different devices in its product coding system.[1] They are the products of an industry with sales totaling more than $31 billion annually.[2]

Medical devices run the gamut from the very simple to the extremely complex, from common household items such as thermometers and bandages to kidney dialysis machines and implantable heart valves. Devices such as artificial hips, intraocular lenses, and hearing aids improve the independence and quality of life of many. Diagnostic devices such as CAT (computerized axial tomography) scanners have increased the speed and accuracy of diagnosis and, in some cases, have replaced more dangerous and painful procedures.

The principal statute under which FDA regulates devices is the Federal Food, Drug, and Cosmetic Act of 1938, as amended by the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990.[3] FDA employs three principal programs to ensure the safety and effectiveness of medical devices: (1) premarket review, (2) good manufacturing practices (GMP) program, and (3) postmarketing surveillance. Premarket review consists of checks, reviews, and controls applied before new devices are produced and made available to the public. Under the 1978 GMP regulation, FDA monitors and enforces quality assurance practices and standards in manufacturing to prevent the production and marketing of defective devices. Postmarketing surveillance is a monitoring system designed to provide an early warning of device problems that become evident after the

[1]Section 201(h) of the Federal Food, Drug, and Cosmetic Act of 1938, as amended by the Medical Device Amendments of 1976, defines "medical device" as an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, that is (1) recognized in the official National Formulary or the U.S. Pharmacopeia or any supplement to them; (2) intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, in humans or other animals; or (3) intended to affect the structure or any function of the human body or bodies of other animals, and that does not achieve any of its primary purposes through chemical action within or on the body and does not depend upon being metabolized in order to achieve any of its primary purposes. The effect of the amendments was to enlarge the 1938 definition of "device" to include (1) devices intended for use in the diagnosis of conditions other than disease, such as pregnancy; (2) in vitro diagnostic products; and (3) specific products previously regulated as new drugs, including soft contact lenses, bone cement, and sutures.

[2]Health Industry Manufacturers Association, Report No. 91-2, "Competitiveness of the U.S. Health Care Technology Industry," based upon unpublished data from the U.S. Department of Commerce.

[3]The Safe Medical Devices Act of November 28, 1990, addressed many of the implementation problems associated with the 1976 amendments. We did not examine FDA's implementation of this most recent act.

devices are in general use. All three regulatory programs are primarily the responsibility of FDA's Center for Devices and Radiological Health (CDRH).

Three Device Classifications

The centerpiece of the 1976 amendments was its classification of three degrees of potential risk associated with medical devices. Each device was to be classified according to extent of control necessary to ensure its safety and effectiveness. All devices that were marketed before the amendments were to be assigned to one of three classes by FDA, based upon recommendations of extra-agency medical specialty panels.[4]

Class I, or "low-risk," devices are subject to minimum regulation. General controls such as the registration of manufacturers, premarketing notification, requirements for good manufacturing practices, and prohibitions against adulteration and misbranding are judged sufficient to provide reasonable assurance of safety and effectiveness.[5] This class includes devices such as tongue depressors, elastic bandages, bed pans, and device support apparatus such as headstraps and breathing tube cleaning brushes.

For class II, or "medium-risk," devices, the medical panels determined that general controls were not sufficient to provide reasonable assurance of safety and effectiveness, but that available scientific information was sufficient to establish performance standards that could provide such assurances. According to the 1976 amendments, FDA was required to develop and establish performance standards that all class II devices must achieve to be approved for marketing.[6] This class of device includes items such as syringes, hearing aids, resuscitators, airway pressure meters, and electrocardiograph machines.

Class III, or "high-risk," devices are the most rigidly controlled. General controls were judged insufficient to provide reasonable assurances of their safety and effectiveness, and sufficient information did not exist to

[4]According to FDA's device coding and classification scheme, 4,034 different devices have been classified. Class I products account for 1,722 product codes; class II's account for 1,909; class III's account for 403. In addition, 240 products are currently unclassified, and 71 have had classification postponed.

[5]FDA distinguishes between manufacturing establishments and owner-operators, who can operate more than one establishment; however, we use the term "manufacturer" in this study to refer to both owner-operators and establishments, unless otherwise noted.

[6]The 1990 Safe Medical Devices Act streamlined procedures required for FDA to establish performance standards and encouraged the agency to use voluntary industry standards. The 1990 act also authorized the use of other special controls for class II devices such as special postmarketing surveillance, patient registries, guidelines, recommendations, and other appropriate actions as FDA deems necessary to provide reasonable assurance of safety and effectiveness.

establish performance standards. Instead, class III devices must be approved before marketing if FDA has promulgated approval regulations that are specific for each device type. These devices are life-supporting or life-sustaining; they are substantially important in preventing the impairment of human health; or they present a potentially unreasonable risk of illness or injury. They include items such as cardiac pacemakers, defibrillators, arrhythmia alarms, artificial heart valves, and automated blood cell separators.

As the 1976 amendments have been implemented, compliance with and enforcement of the GMP regulation have assumed critical importance. At the time of our study, FDA had not yet issued any standards for class II medical devices. Furthermore, it had required manufacturers to submit proof of safety and effectiveness for only about 9 percent of class III devices marketed before 1976.

Consequently, the majority of medical devices, in all classes, reach the market under section 510(k) of the act (the premarket notification process).[7] Under this section, at least 90 days before marketing its device, a manufacturer must demonstrate that it has the same intended use as a preamendment device and that it has the same technological characteristics. Alternatively, a device may have different technological characteristics but it cannot raise different questions of safety and effectiveness, and information submitted demonstrates that the device is as safe and effective as a legally marketed device.

The 510(k) review process may require review of a device's operating principle, design and specifications, energy source, processing procedures, sterilization, and accuracy, precision, specificity, and sensitivity in performance. Significant differences must also be explained. FDA may request more information or find that the device is or is not "substantially equivalent."

If FDA finds the device substantially equivalent, it may be placed in interstate commerce. Fewer than 2 percent of the submissions are found to be not substantially equivalent.[8] FDA officials point out that a finding of substantially equivalent does not represent and should not be construed as a

[7]See our reports entitled Medical Devices: Early Warning of Problems Is Hampered by Severe Under Reporting, GAO/PEMD-87-1 (Washington, D.C.: Dec. 19, 1986) andMedical Devices: FDA's 510(k) Operations Could Be Improved, GAO/PEMD-88-14 (Washington, D.C.: Aug. 17, 1988).

[8]According to FDA, another 10 percent of 510(k) submissions are withdrawn by the manufacturer or not resubmitted after FDA has requested additional information.

statement of a device's safety and effectiveness. It means only that the device is substantially equivalent to a preamendment class I, II, or III device.[9]

In general, preamendment class II and III devices are cleared for marketing by FDA without showing evidence of their safety and effectiveness, nor are they tested by FDA to product quality standards. Consequently, the GMP compliance program has been FDA's only attempt to broadly assess safety and effectiveness before medical devices reach the market.

Quality Assurance Policy

Section 520(f) of the act, as amended, authorizes FDA to promulgate regulations that specify quality assurance practices in the manufacture, packaging, storage, and installation of all finished medical devices, with the goal of preventing the distribution of defective devices that are unsafe or ineffective for their intended use. The GMP regulation, promulgated in July 1978, should serve as a framework within which manufacturers can incorporate their individual quality assurance programs. (See appendix II for the complete text of the GMP regulation and appendix III for a detailed outline.) FDA has since issued one guideline to manufacturers (on process validation) and one recommendation (on preproduction quality assurance); however, the GMP regulation has not been substantially revised since its promulgation.[10]

[9]Since 1976, devices found to be substantially equivalent to products on the market before 1976 reach the market with no additional premarket review. A postamendment device that is not substantially equivalent to pre-1976 products must have premarket approval (a much more rigorous process than 510(k) review) or be specifically classified as class I or II.

[10]FDA Center for Devices and Radiological Health, Division of Compliance Programs, Preproduction Quality Assurance Planning: Recommendations for Medical Device Manufacturers (Rockville, Md.: Sept. 1989); FDA Center for Drugs and Biologics and Center for Devices and Radiological Health, Guideline on General Principles of Process Validation (Rockville, Md.: May 1987).

In process validation, a manufacturer establishes evidence that provides a high degree of assurance that a specific process will consistently produce a product that meets its predetermined specifications and quality characteristics. Preproduction quality assurance, or "design review," is a manufacturer's program for reviewing device designs to ensure their reliability, safety, and effectiveness before the devices actually go into production. See chapter 2 for further discussion.

The GMP regulation requires medical device manufacturers to establish a quality assurance program that includes the traditional quality-control functions of product testing and inspection. It also includes requirements for buildings, equipment, device evaluation, and record-keeping among its major subparts.

FDA currently assesses compliance with the GMP requirements through a program of mandated biennial inspections of manufacturers' premises for class II and III devices. This congressional mandate is commonly called the "statutory obligation." Class I manufacturers should also be inspected, but there is no prescribed schedule. In addition, FDA conducts "for cause" inspections when they are warranted by complaints or other evidence of problems with devices.

The results of several recent congressional inquiries and other analyses have raised questions about the effectiveness of the GMP program in preventing the marketing of unsafe and ineffective medical devices. For example, congressional hearings in 1989 and 1990, as well as our 1990 evaluation have suggested that potentially serious gaps exist in the current regulation and in its implementation.[11]

Objectives, Scope, and Methodology

Objectives

On January 19, 1990, the House Subcommittee on Oversight and Investigations asked us to provide them with a review and analysis of the structures and procedures FDA has established to promote good manufacturing practices for medical devices. The Subcommittee requested that we pay particular attention to industry practices and FDA surveillance activities relating to the GMP requirements on process validation, the status of industry and FDA efforts in preproduction quality assurance, and the status of GMPs for manufacturers of critical devices.[12]

[11]See Medical Device Safety, Hearings Before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, 101st Cong., Nov. 6, 1989, and July 17, 1990, and Medical Devices: Underreporting of Serious Problems With a Home Apnea Monitor, GAO/PEMD-90-17 (Washington, D.C.: May 31, 1990).

[12]The GMP regulation identifies "critical devices" as those that are intended for surgical implant into the body or to support or sustain life. Their failure to perform when used properly in accordance with instructions provided in the labeling can be reasonably expected to result in a significant injury to the user. At the present time, 92 class III devices and 81 class II devices have been identified as critical.

In subsequent discussions with the Subcommittee staff, we agreed on two objectives and formulated evaluation questions for each of them. Our first objective was to develop an analytical description of the regulatory program that FDA has established to define and enforce quality assurance in device manufacturing. To meet this objective, we established the following evaluation questions:

1. What are the current and proposed GMP requirements?

2. How do requirements differ for critical devices?

3. How are GMP inspections conducted?

4. What are the qualifications of GMP inspectors?

5. How is GMP compliance enforced?

We wanted to determine how the current GMP program has been structured as a preliminary step toward understanding and assessing program implementation. In particular, we wanted to review the validity and general acceptance of GMP requirements, the appropriateness of official inspection and compliance procedures, and the technical competence of GMP inspectors, as these factors determine GMP program effectiveness.

Our second objective was to provide a qualitative and statistical review of FDA's inspections and compliance actions. To meet this objective, we established the following evaluation questions:

1. How often does FDA inspect device manufacturers?

2. What are the nature and scope of GMP-related violations?

3. What compliance actions have FDA and device manufacturers taken in response to GMP violations?

In meeting this objective, we wanted to assess how GMPs have been implemented and how well implementation meets statutory requirements and related effectiveness criteria, including FDA's and industry's response to correct GMP problems identified during inspections. This response is another critical factor determining program effectiveness.

Scope

The GMP program applies to the manufacture of all classes of medical devices. In this study, however, we focused primarily on manufacturers of class II and III devices. These devices support the most critical body functions and consequently they involve the greatest risk of injury and death should they fail. We also gave special consideration to critical devices as a category of devices subject to special GMP controls. We reviewed GMP program data bases from 1978 through 1990, but focused our analysis mainly on fiscal year 1984 and after.[13] Field work for this project was undertaken from September 1990 to January 1991 in accordance with generally accepted government auditing standards.

Methodology

Our two objectives required different kinds of information from many sources. To understand the 1976 Medical Device Amendments and the Safe Medical Devices Act of 1990, we reviewed the statutes, their legislative histories and related articles and documents. Background information and critiques on the GMP regulation were obtained from official FDA documents and through structured interviews with former and current FDA officials as well as knowledgeable individuals in the private sector.

GMP program data were obtained from FDA as hard copy and electronic media, including reports of GMP violations, reports of FDA regulatory actions associated with GMP violations, and selected records from FDA's inspection program data base. We did not evaluate the internal controls of the computer system that produced the data reports. However, we did selected validation of FDA data reports by comparing the same records from different FDA source files to check for missing data and inconsistencies.

We also surveyed 325 field inspectors to obtain information about their qualifications related to quality assurance methods and device technology.[14] In the same survey, we asked inspectors for their opinions concerning possible improvements in the GMP program. We obtained an 85-percent response rate from the questionnaire.

The nature of the data we collected required both qualitative and quantitative analysis. We systematically reviewed the documents describing implementation and operation of the GMP program and

[13]FDA's data definitions and systems changed in 1984, making it difficult to access and analyze pre-1984 data.

[14]Details of our sample selection process are presented in appendix IV. In this report, we use the term "inspectors," although FDA makes a distinction between inspectors and investigators.

conducted structured interviews with FDA officials to clarify, confirm, and supplement the documentary evidence. We used procedures available from a relational data base program (Paradox) and the Statistical Package for the Social Sciences for analysis of FDA data reports and files. Our analysis included frequencies, cross-tabulations, and associated statistical tests.

We obtained formal written comments from HHS on a draft of this report and revised our draft to take account of them, as appropriate. The final content of the report also benefited from the reviews and comments provided by a panel of experts. (See appendix VI for a complete list of panel members.)

Report Organization

The remainder of the report is organized as follows: chapter 2 describes the GMP regulatory requirements; chapter 3 describes the structure and procedures that constitute GMP program implementation, including the qualifications of GMP inspectors; chapter 4 presents program results in terms of the frequency of GMP inspections, number and types of problems identified in GMP inspections, and FDA and industry responses to GMP deficiencies; and chapter 5 contains our conclusions and recommendations, as well as agency comments and our response.

Regulatory Requirements

Introduction

FDA promulgated the Good Manufacturing Practices (GMP) regulation in July 1978. The regulation defines GMP requirements in terms of over 50 broad quality assurance objectives that can be reviewed during GMP inspections of manufacturing facilities. With the exception of device design, they apply to every activity necessary to prevent the manufacture of defective medical devices. Furthermore, they apply to the manufacture of all finished medical devices for human use, unless a manufacturer has received an exemption or variance.[1]

This chapter describes GMP requirements as defined in the 1978 regulation and their subsequent evolution over time, including the collateral development of an FDA guideline on process validation and its recommendation on preproduction quality assurance (PQA). It addresses the first two evaluation questions under our first objective: to develop an analytical description of the regulatory program that FDA has established to define and enforce quality assurance in device manufacturing. The two evaluation questions are:

1. What are the current and proposed GMP requirements?

2. How do requirements differ for "critical devices"?

GMP Requirements in the 1978 Regulation

The GMP regulation is divided into 10 subparts. (See appendix II for a copy of the regulation and appendix III for a summary outline.) The first describes the scope and authority of the regulation and defines terms. As shown in the first column of table 2.1, the last nine subparts present requirements for device manufacturing operations.

[1]Current exemptions include only certain class I devices.

Table 2.1: The Organization and Evolution of GMP Requirements

Subpart	Examples of 1978 requirements	Examples of 1991 requirements
A. General Provisions		
B. Organization & Personnel	Have adequate organization and personnel to ensure compliance with the regulation	No change
C. Buildings	Have adequate design and space to facilitate cleaning, maintenance, and necessary operations	No change
D. Equipment	Have adequate equipment to facilitate maintenance, adjustment, and cleaning	Adequate equipment for intended use
E. Control of Components	Adhere to written procedures for acceptance of components	No change
F. Production & Process Controls	Adhere to written procedures to control production processes and to change them	Adequate process validation and change control
G. Packaging & Labeling Control	Have adequate controls to maintain label integrity and to prevent labeling mixups	No change
H. Holding, Distribution, & Installation	Adhere to written procedures for warehouse control and distribution	No change
I. Device Evaluation	Adhere to written procedure to investigate devices that fail after release for distribution	Adequate failure investigation, including corrective actions
J. Records	Adhere to complaint review procedures	Adequate complaint analysis procedures

GMP requirements apply to all medical devices except those with an exemption or variance. However, according to official FDA guidance, their application should be flexible. That is, required quality assurance activities should be proportional to the potential for errors in manufacturing and to the resulting risk of injury or death to patients or users. Also, the requirements themselves are broadly defined in terms of quality assurance objectives (see column 2 of table 2.1), and their nonspecificity is considered to be consistent with the idea of flexibility.

The examples of requirements listed in column 2 illustrate the two basic GMP performance criteria, the first less stringent than the second. Less stringent "adherence" criteria only require that manufacturers have a written quality assurance plan and that they adhere to it. According to FDA's Center for Devices and Radiological Health (CDRH), these criteria are much easier to translate into operational inspection guidelines and performance requirements. Many adherence criteria can be verified by merely following a paper trail, if not by simply having a manufacturer's representative run down a checklist of quality assurance activities.

"Adequacy" criteria are potentially more stringent because they often require manufacturers to meet industry standards and practices both in

terms of their technical details and in terms of their overall reliability.[2] Adequacy criteria authorize broader as well as more intensive inspections but they are also much more difficult to translate into operational terms. Consequently, adequacy criteria may not, in practice, be different from adherence criteria unless inspectors can translate them into operational requirements for specific device manufacturing processes. Effective translation requires extensive, up-to-date technical knowledge. Such translation may also increase variation among inspectors in the content and quality of inspections.

The Evolution of Current GMP Requirements

Preventing the production and distribution of defective devices has remained the objective of the GMP program since 1978, but FDA's interpretation of some GMP requirements has changed. According to CDRH, it was originally believed that compliance with the requirements could be achieved by using reactive adherence criteria. That is, FDA would monitor device manufacturers only to see if they had quality assurance procedures and if these were followed. Little attention was paid to the content of these procedures.

Over time, as FDA gained experience conducting GMP inspections and as their monitoring of results showed recurring device defects, the official interpretation of regulatory requirements shifted toward the more stringent adequacy requirements. The overall pattern of this shift is illustrated by comparing requirements in the second and third columns in table 2.1. Three of the most significant new adequacy criteria involve process validation, change control, and failure investigation. These are described below.

Process Validation

Process validation was not specifically mentioned in the 1978 regulation. Nevertheless, according to FDA an official "guideline" issued in 1987 for manufacturers of drugs and medical devices established process validation as a requirement of the Good Manufacturing Practices regulation.[3] Process validation involves the review of specific equipment, processing subsystems, and representative product sampling to establish the reliability of

[2]Industry performance criteria may exist as formal standards published by official industry associations, and some of these may also be sanctioned by the American National Standards Institute. However, performance criteria may also be unofficial, based only upon the inspector's experience inspecting similar devices.

[3]The device GMP program has issued only one official guideline. See FDA CDRH, Guideline on General Principles of Process Validation (Rockville, Md.: May 1987). According to FDA, regulations are binding requirements; guidelines are less binding than regulations but over time they may become de facto regulations; and recommendations are least binding or more like advisory notices.

manufacturing processes; that is, to establish that they will consistently produce a device that meets the predetermined specifications and quality attributes. The guideline also calls for timely revalidation whenever changes are made in equipment, processing, or product specifications, and for documentation of all validation activities.

Process validation is particularly critical when the quality of a process cannot be verified by subsequent product inspection and testing. This is the case when the large number of products produced by each production unit precludes testing each one (e.g., rubber gloves); when the cost of product testing is prohibitive (e.g., testing for potentially lethal protein impurities in the latex cuff of barium enema kits); and when necessary testing would damage the device (e.g., testing the glue holding catheter tips and balloons or the glue and structural elements within emergency ventilators).

Change Control

Change control is closely related to process validation in that both involve review of equipment and processes to ensure a consistent output of devices that meet predetermined specifications. However, process validation is ongoing, while change control procedures apply before changes are made in device design or production processes. The regulation calls for adherence to formal change control procedures. However, the current GMP compliance manual states that the change control procedures must be adequate. A classic example of both inadequate change controls and inadequate process validation occurred in the manufacture of the Shiley mechanical heart valve. Over a 5-year period starting in 1979, the manufacturer made a series of product and process changes to prevent valve breakage. Despite these changes, the valves continued to break and were associated with 178 deaths.[4]

Failure Investigation

Failure investigation is also related to process validation in the sense that data on device failures should be used to reconsider whether the equipment and the manufacturing process are working reliably. Current failure investigations should be conducted according to a written analysis program that is adequate to identify trends and causes of problems, to determine the significance of any defect, and to establish corrective

[4]See U.S. House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, Committee Print 101-R, The Bjork-Shiley Heart Valve: "Earn As You Learn," subtitled, "Shiley Inc.'s Breach of the Honor System and FDA's Failure in Medical Device Regulation," Feb. 1990.

actions. A problem with anesthesiology machines in 1983 and 1984 provides an example of inadequate failure investigation. Sticking valves had been brought to the attention of the manufacturer's field representatives as a potential risk, but the problem was not corrected before patients sustained serious injuries and some deaths occurred.

Were New Adequacy Requirements Evaluated?

Significant changes made in the GMP program create the opportunity to assess their impact by tracking program activities and results before and after the changes are made. These new interpretations of the GMP regulation substantially increased the potential scope and detail of GMP inspections; however, no formal assessment of their impact was made. Consequently, it is not known what difference they have made either in terms of the conduct of inspections, the operations of device manufacturers, or the quality of medical devices.

FDA'S Proposed Revisions to the GMP Regulation

Recently, FDA has proposed revisions to the 1978 regulation that would codify current adequacy requirements as well as add new ones.[5] The new GMP requirements reflect dual concerns—increasing the safety and effectiveness of medical devices and recognizing the increasing importance of the global market for medical devices. The most significant proposed new requirements involve preproduction quality assurance and quality assurance for suppliers of components purchased by device manufacturers and for servicing of used devices by the manufacturer.[6]

[5]FDA CDRH, Suggested Changes to the Medical Devices Good Manufacturing Practices Regulation: Information Document (Rockville, Md.: Nov. 1990).

[6]The 1990 Safe Medical Devices Act specifically authorizes FDA to regulate preproduction quality assurance.

The 1989 Recommendation and Proposed PQA Requirements

In September 1989, FDA published an official "recommendation" for device manufacturers to have preproduction quality assurance.[7] According to the recommendation, manufacturers should follow 12 steps to ensure the quality of their device designs.[8] The need for PQA was based upon an analysis of medical device recalls for fiscal years 1983 through 1988.[9] GMP problems caused 47 percent of these recalls, while 44 percent were caused by design defects.[10] FDA concluded that most of the design-related problems could have been avoided had manufacturers implemented proper preproduction quality assurance practices.[11]

This conclusion and FDA's new emphasis on quality assurance in the preproduction stage of device manufacturing may be interpreted as an acknowledgment by the agency that its current GMP program requirements, with their exclusive focus on manufacturing, are necessary but not sufficient to ensure the production of safe and effective medical devices. Under current GMP requirements, a superior production quality assurance process can, at best, ensure production of the medical devices as designed. However, if there is an inherent flaw in the device design, the current GMP program can also ensure the production of a problem device.

In the proposed GMP requirements for PQA, we found both adherence and adequacy inspection criteria. Requirements specify that device manufacturers should adhere to formal controls for planning the design effort, formal output of the design effort (e.g., drawings), formal approval of these outputs, documented design changes, simulated end-use testing, and a formal PQA quality manual. These design controls should also ensure that

[7]FDA CDRH, Division of Compliance Programs, Preproduction Quality Assurance Planning: Recommendations for Medical Device Manufacturers (Rockville, Md.: Sept. 1989).

[8]According to the recommendation, preproduction quality assurance practices should include reviews of: (1) PQA organization, (2) device specifications, (3) design review procedures, (4) reliability, (5) component parts and materials, (6) software, (7) labeling, (8) design transfer to manufacturing, (9) certification of production units, (10) personnel, (11) instrumentation tests, and (12) quality monitoring during manufacturing.

[9]FDA CDRH, Device Recalls : A Study of Quality Problems (Rockville, Md.: Jan. 1990). In addition to employing the term "recall" to refer to the removal of a device from the market or its return to the manufacturer for repair, FDA also uses the word to denote field repairs, hazard warnings, the correction of labeling or promotional materials that the agency considers to be in violation of the laws it administers, and other situations.

[10]The remainder were for miscellaneous causes such as failure to control radiation from sunlamps, misbranding, and other problems that could not be attributed to manufacturing or design problems.

[11]The Inspector General of the Department of Health and Human Services (HHS) also found that design problems were prevalent in a more recent study of selected recall cases. See HHS Office of Inspector General, Office of Evaluation and Inspections, FDA Medical Device Regulation From Premarket Review to Recall (Washington, D.C.: Sept. 1990).

design requirements and design outputs are adequate for their intended use.

Quality Assurance for Suppliers and Servicing

Quality assurance requirements for purchased components and services are proposed because a significant number of recalls have resulted from defective, purchased inputs. Proposed purchasing requirements involve documentation of a supplier's ability to provide quality components and services that are adequate for their intended use. In making this proposal, FDA asserts that each supplier should have demonstrated capability in quality assurance because quality cannot be inspected "into" components and services as they are delivered to finished device manufacturers.

Quality assurance requirements for servicing are proposed because improper servicing can affect a device's safety and effectiveness. The proposed servicing requirement is to have devices returned for servicing and repair reviewed and evaluated by a formally designated unit in accordance with written procedures. Among other things, the evaluation should include a trend analysis of malfunctions, and when trends are detected, they should be treated as complaints and processed accordingly.

This new servicing requirement applies only to manufacturers of finished devices. Servicing done by hospitals and other providers, as well as by third parties, will remain unregulated. This is a significant omission because device maintenance and repairs are often done by someone other than the manufacturer. Furthermore, if regulation of servicing done by the manufacturer makes sense, then it should make sense to regulate servicing done by anyone else. In fact, it may be even more important to regulate others because they do not have the manufacturer's experience with product design and manufacturing nor an incentive to meet competition from manufacturers of similar devices.

Global Market and Industry Competitiveness

One of the major trends in the global market is the adoption of international quality assurance standards for manufacturing. The medical device industry is no exception to this trend. One purpose for the new requirements is to harmonize GMP requirements to the "9001" standard, published in 1987 by the International Standards Organization (ISO). According to FDA, harmonization is important in order to minimize confusion among alternative quality assurance standards and to facilitate "mutual recognition" of inspection results among alternative inspection

organizations. The latter precludes expensive, duplicate inspections and eliminates an important nontariff barrier to international trade.

Furthermore, the ISO standards are being used by the European Community (EC), a major market for U.S. medical device manufacturers, as the basis for harmonizing quality system standards across EC member countries. To maintain their positive trade balance and its competitive position in the global medical device market, U.S. medical device exporters will have to conform to these standards after 1992.

Critical Devices

In addition to GMP requirements for all medical devices, there are nine special requirements for critical devices. (See appendix III.) For example, acceptance procedures for components in critical devices must have written sampling, testing, and inspection procedures that are not required for noncritical devices. Similarly, special written procedures are required for reprocessing devices that fail their final production tests and for investigating why such failure occurred. A written account of the production and distribution history of each lot of critical devices must contain special control numbers and signatures of production line inspectors in order to track down problems if they arise and to alert users.

With the exception of requirements necessary to trace devices through market channels, FDA's proposed revisions to the 1978 GMP regulation would eliminate special requirements for critical devices by extending them to all devices. Many device manufacturers believe that this extension is a major expansion of the regulation; however, FDA believes that this change would not significantly increase the GMP regulatory burden for noncritical device manufacturers.

Summary

FDA defines GMP requirements broadly in terms of quality assurance objectives that apply to all medical devices and to all activities and inputs necessary to prevent device defects. According to FDA guidance, the application of these requirements should be flexible and in proportion to the potential for errors in manufacturing and the resulting risk of injury or death.

GMP requirements are defined in terms of either the less stringent adherence or potentially more stringent adequacy criteria. Adherence criteria simply require manufacturers to have and to adhere to a written quality assurance program. Adequacy criteria are potentially more stringent, but much more difficult to translate into operational guidelines, because they

require manufacturers to conform to industrywide and often highly technical quality standards. The difference between the two, in practice, depends upon whether FDA inspectors have the technical background and experience to recognize industry quality standards and to translate them into operational performance criteria for specific device manufacturers.

Since the initial promulgation of the GMP regulation in 1978, FDA has increased the number of adequacy criteria. However, the agency failed to assess the impact of these new adequacy criteria by monitoring program activities and outcomes before and after these changes were made.

The trend toward increasing adequacy criteria would continue with FDA's proposed revisions to the 1978 regulation. Specifically, these include adequacy requirements for preproduction quality assurance, suppliers of services and components, and servicing of used devices by manufacturers. These three additional requirements would also harmonize GMP requirements with international quality assurance standards in order to facilitate exports by U.S. manufacturers. However, the extension of requirements to servicing of used devices is incomplete because it omits servicing done by third parties.

The Organization of GMP Inspections and Compliance Enforcement

The 1976 Medical Device Amendments mandate on-site inspections of all medical device manufacturers and biennial inspections for manufacturers of class II and III devices.[1] These inspections serve as the agency's principal means for implementing the GMP regulation and its principal source of information about industry compliance with the regulation. Based upon inspection results, FDA also initiates compliance actions against manufacturers with the most serious GMP violations.

This chapter addresses the last three questions under our first objective, which was to develop an analytical description of the regulatory program that FDA has established to define and enforce quality assurance in device manufacturing. The evaluation questions are:

1. How are GMP inspections conducted?

2. What are the qualifications of GMP inspectors?

3. How is GMP compliance enforced?

Organization of the GMP Program

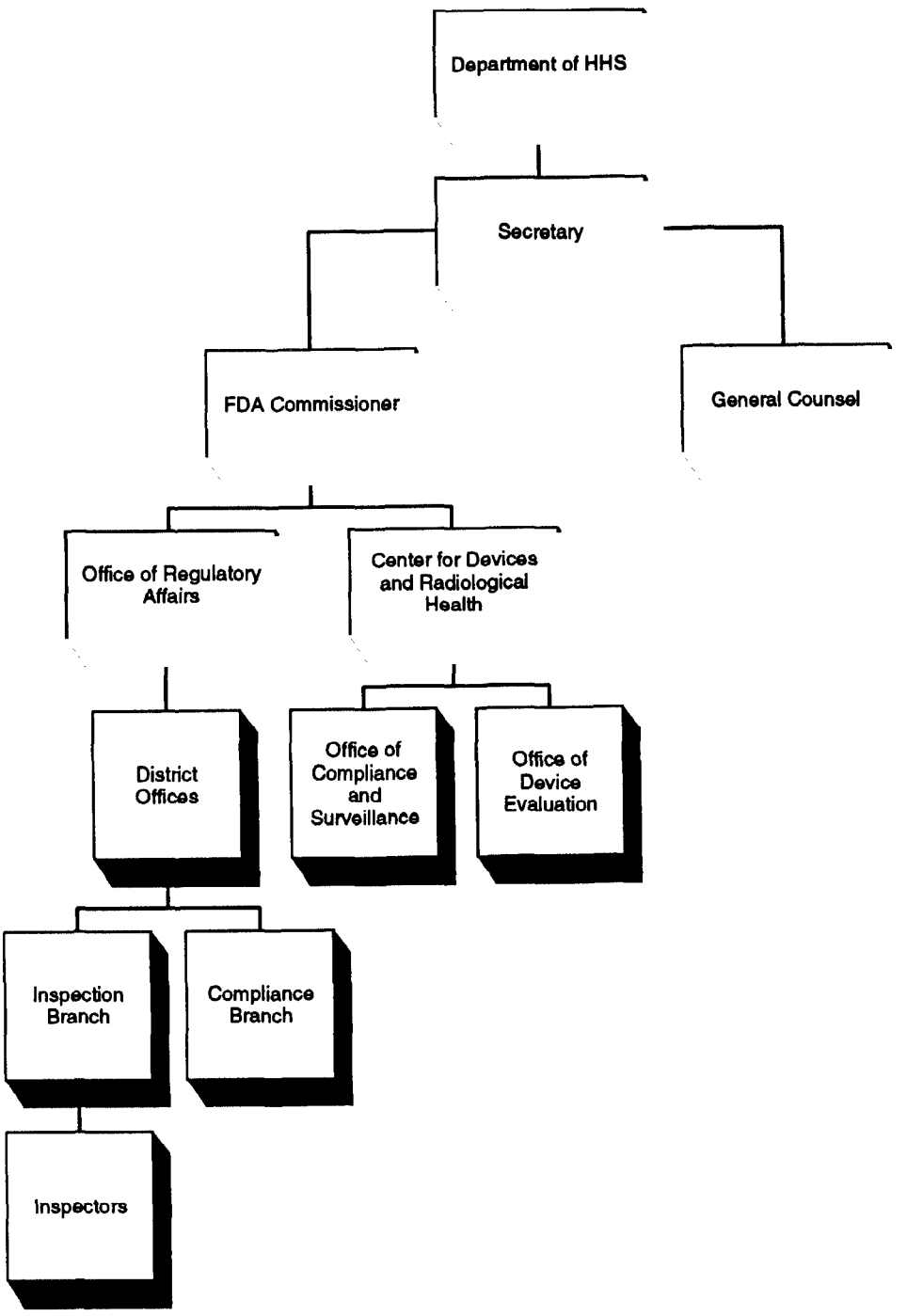
The Center for Devices and Radiological Health (CDRH) and the Office of Regulatory Affairs are the two principal operating units within FDA that administer the device GMP program. Within CDRH, the Office of Compliance and Surveillance has primary responsibility for device GMPs. Also within CDRH, the Office of Device Evaluation reviews and approves new devices for market introduction, based in part on the results of GMP inspections of manufacturers.[2] A third unit, the Office of General Counsel under the Secretary of the Department of Health and Human Services (HHS), must approve the most severe GMP compliance enforcement actions.[3] (See figure 3.1.)

[1]FDA policy specifies that these shall be GMP inspections, performed by FDA inspectors.

[2]CDRH also has a Division of Small Manufacturers Assistance, which provides technical and other nonfinancial assistance to help device manufacturers comply with GMP requirements. These activities include conducting workshops, developing and distributing publications, and answering telephone inquiries.

[3]We refer to the associate general counsel, Food and Drug Division, as the FDA general counsel.

Figure 3.1: Organization of the Device GMP Program



GMP regulations and compliance programs are developed and broadly managed by the Office of Compliance and Surveillance, which defines the processes and activities to be regulated, the requirements to be met, and the enforcement actions to be taken if district offices report GMP violations. This office is also responsible for monitoring the medical device industry and its manufacturing practices.

The Office of Regulatory Affairs is responsible for the administration of FDA's 21 district offices located within the United States and Puerto Rico. Together, this office and district offices are responsible for all FDA inspections, including food, drugs, and blood banks as well as devices. Each district office hires its own inspectors and compliance officers and each schedules and performs on-site compliance inspections for all FDA-regulated facilities in its district. The office schedules and performs GMP inspections of foreign manufacturers as well, using a cadre of inspectors based in the district offices. Finally, the office is also responsible for training the field inspection staff.

GMP Inspection Process

Several conditions may trigger the initiation of a GMP inspection, including the 2-year statutory obligation, a follow-up needed to confirm the correction of a previously identified problem, or a potential device problem that has been reported to FDA by users or competitors.[4] Much less frequently, an inspection occurs when a manufacturer notifies FDA of its intent to go into production at a new site or when a manufacturer submits a premarket approval application for a new class III device.

An inspection starts with an FDA inspector making an unannounced visit to the manufacturing site, at which time the manufacturer must allow the inspector admittance and provide all pertinent GMP documentation. Inspections may include all records, files, papers, processes, controls, and facilities, but not financial data or research not directly related to the product being inspected. The inspector may spend as little as one day or as much as a month at a facility, depending upon the complexity of the manufacturing process and potential quality assurance violations.

[4]The 1990 act requires, for the first time, that medical-care facilities report all device-related, serious illnesses and injuries or deaths to the manufacturer and report deaths directly to FDA, along with the number of reports sent to each manufacturer. Depending upon FDA implementation, these new reports could generate vast new data for targeting GMP inspections to manufacturers, devices, and manufacturing processes that are most likely to have quality assurance problems.

Track I Inspections

Since 1986, FDA has employed a two-track inspection strategy. Track I inspections are limited to a subset of GMP requirements that involve mainly looking at the device rather than at the manufacturing process. An inspection is a track I if a pre-inspection review indicates that a comprehensive (track II) inspection has been conducted within the last 2 years and if that prior inspection did not reveal violative behavior that was not corrected and verified by a follow-up inspection. The pre-inspection review should also indicate no GMP-related recall since the last GMP inspection and no significant problems reported in the Device Experience Network, Medical Device Reports, or other FDA data that may identify potential device defects.[5]

Track I inspections cover only GMPs that must be reviewed on every inspection. In order, these are:

- adequate complaint handling, including documentation of complaints, trend analysis, and corrective actions when appropriate;
- adequate failure investigation and analysis, including documentation that the cause of failure and its significance was determined, and that appropriate corrective action was taken;
- adequate control of any changes in device or production process design, including documentation of procedural steps, official approvals, and reliability testing;[6]
- adequate procedures for auditing the entire production process, including identification of stages with greatest potential for generating device defects; and
- quality assurance system changes, including supporting rationale and documentation that any changes ensure safety and effectiveness.

If the track I review reveals no significant quality assurance problems, then the inspection may be terminated.[7] An inspector is free to conduct an in-depth review of specific areas or systems, but the inspection remains a track I inspection. If significant adverse findings are made during a track I

[5]For a description of FDA's systems for manufacturer reporting of device-related incidents, see Medical Devices: FDA's Implementation of the Medical Device Reporting Regulation, GAO/PEMD-89-10 (Washington, D.C.: Feb. 17, 1989).

[6]Since changes in device and process design involve the design process, change control involves requirements similar to those outlined in the 1989 recommendation on PQA that ensure the safety and effectiveness of new designs.

[7]FDA defines significant quality assurance problems as those that are likely to have an adverse effect on the safety or efficacy of a device given its intended use.

inspection, then the inspection is converted to a track II or comprehensive inspection.

Track II Inspections

The procedures for performing a track II, comprehensive GMP inspection are less precise than for a track I inspection. According to the Office of Compliance and Surveillance, the inspector is supposed to review and evaluate all of the components of the manufacturer's quality assurance system that fall within the jurisdiction of the device GMP regulation. GMP inspections may not involve all production processes for all devices produced by a manufacturer if the same process is used to make several devices.

In this situation, FDA categorizes manufacturing processes into "profile classes." Profile classes are generic manufacturing activities such as chemical sterilization, plastic fabrication and assembly, or electronic assembly. All profile classes are inspected. When a profile class is used at different locations within a plant, to make different devices, inspectors generally review the location that makes a device that presents the greatest health and safety risk.

Since there are over 50 different quality assurance criteria that can be verified at various levels of detail, inspectors exercise discretion in selecting targets for inspection that are most likely to reveal significant GMP violations. According to quality assurance experts inside and outside of FDA, inspectors generally follow a problem-oriented strategy. That means looking for telltale signs of potential device or production process problems. These signs are treated like loose threads on a seam. Each is "pulled out" to see if anything important unravels.

Coordination With Premarket Review

In addition to track I and II inspections, CDRH has recently revised requirements for premarket approval for class III devices for which FDA had promulgated premarket approval requirements.[8] These include about 9 percent of the different device types in this class. Since December 1990, premarket approval has involved an "initial" and a "follow-up" GMP inspection.

[8]New class III devices must have premarket approval by FDA if they are not substantially equivalent to preamendment class III devices or if FDA has promulgated device-specific premarket approval requirements. See FDA, CDRH, DCP, Medical Device Premarket and Postmarket Inspections (Rockville, Md.: Sept. 1990).

The initial premarket inspection occurs before a class III device is approved. Like track II inspections, it covers all profile classes, but it also goes further to assess process validation based upon a comprehensive assessment of device and process specifications. Results from this initial inspection also have a greater impact on manufacturers than other GMP inspections because the device cannot be marketed without the district office's certification that the manufacturer can produce devices according to specifications contained in its premarket approval application. A follow-up inspection, occurring about 8 months after the introduction of the device, serves to verify that the production plans reviewed during the initial inspection were implemented.

The coordination of GMP inspections with premarket approval is important because, according to the literature on manufacturing reliability, the frequency of design and manufacturing defects is greatest when a product is first manufactured. However, the coordination with premarket approval contrasts with the lack of coordination for devices that reach the market through the 510(k) review. The overwhelming majority of all classes of devices reach the market through the 510(k) or "substantially equivalent" route, which does not require a GMP inspection.

When the Office of Device Evaluation completes its review of a 510(k) application with a finding of substantial equivalence, the appropriate district office receives a copy of the letter sent to the manufacturer. However, the letter does not help the district office to identify GMP risks in changing technology and to target inspections accordingly.

Partly in response to our previous report and another review of the 510(k) program, FDA recently started a pilot program designed to change the scope and increase the consistency and efficacy of the 510(k) review.[9] It involves 510(k) sterile cardiovascular devices that have been or will be sterilized by a traditional method and that are also implants or that come into direct contact with blood or spinal fluids. According to FDA, the agency is currently exploring the feasibility of expanding the pilot program to include all 510(k) submissions for class III and all other critical devices and to require GMP certification before they can be marketed. In the current pilot program, clearance for marketing is granted even if inspections find that manufacturers are in violation of GMP regulations for sterility.

[9]See FDA's 510(k) Operations Could Be Improved, GAO/PEMD-88-14 (Washington, D.C.: Aug. 17, 1988), and Internal Control Weaknesses in the Food and Drug Administration's Medical Device 510(k) Review Process, A-15-89-00065 (Washington, D.C.: DHHS/OIG, July 1990).

In the pilot program, the Office of Device Evaluation provides the Office of Compliance and Surveillance with information that can be used to trace and assess the manufacturing experience of the manufacturer. The latter office then reviews six central data files for information pertaining to the manufacturer's ability to manufacture sterile devices adequately. If an inspection has not occurred within 2 years, or if the last inspection revealed problems with sterilization, an inspection is ordered.

Preliminary results of the pilot program show that 265 cardiovascular devices have been reviewed, representing about 30 percent of all 510(k) cardiovascular devices and about 3 percent of all 510(k) devices. For 89 of these cases (34 percent), an inspection was ordered. Twenty-nine of these inspections have been conducted, but 37 are overdue.[10]

The number of cases needing an inspection indicates that the pilot program has helped to target GMP inspections. Furthermore, coordination of inspections with market introduction will also improve the effectiveness of the proposed regulation of preproduction quality assurance, because the best time to uncover design defects is before or soon after the device is used. Finally, according to FDA, whether to expand the pilot program to include all high-risk medical devices is currently being explored.

However, expansion of the pilot program to include all high- risk devices is at best a limited substitute for premarket approval certification. While the latter involves a special, more comprehensive inspection immediately before marketing a high-risk device, and a second inspection soon after, the pilot program approach relies on only one, standard GMP inspection—and that may have occurred as long as 2 years before the 510(k) application.

Qualifications of Field Inspection Staff

The effectiveness of the GMP program in finding and correcting quality violations depends in large part upon the inspector who conducts GMP inspections. If the inspector does not identify violations that cause device defects, based upon an understanding of the regulation, the manufacturing operations, and the device being inspected, then FDA cannot take appropriate compliance actions. This section reviews the qualifications and experience

[10]Inspection orders have different priorities. Top priority is given to manufacturers who have had a recent history of GMP violations. These inspections should be conducted within 30 days of an order. High priority is given to manufacturers who have never been inspected. They should be inspected within 60 days. All other manufacturers should be inspected within 90 days.

of inspectors and discusses those factors in relation to assessing device manufacturers' compliance with the GMP regulation.[11]

Each of FDA's 21 district offices hires consumer safety officers as GMP inspectors, based upon allocations from the Office of Regulatory Affairs, and each district office has some latitude in setting qualifications. Our survey found that over 92 percent of device inspectors have bachelor's degrees, and that 72 percent of these degrees are in fields related to the natural sciences, with majors such as biology and chemistry. Seven percent have engineering degrees. Overall, device inspectors have an average of 15 years with FDA, and more than half have at least 9 years' experience doing device inspections.

Although grounding in the natural sciences or engineering may be beneficial, for several reasons it cannot substitute for continuous technical training. First, medical device technologies are diverse, complex, and rapidly changing. According to one of FDA's national device experts, one year away from the industry can render technical knowledge obsolete. Second, the device industry—and especially the export sector—is rapidly expanding and thus pressure to meet foreign competition is increasing the pace of change. Third, the need for technical competence is growing as FDA continues to expand the number of adequacy criteria in the GMP regulation, the criteria that require attention to the technical details of manufacturing processes and device design.

Current FDA Training Policy

The principal form of training available is on the job. However, our data indicate that the value of an inspector's on-the-job experience for device-specific technical training is mitigated by assignment to other FDA compliance programs. "Qualified" inspectors have spent an average of 25 percent of their time doing device inspections; "highly qualified," about 41 percent.[12] The rest of their time is spent on drugs, food, blood banks, and other FDA inspection programs. Thus, we found that even among the most highly qualified inspectors, more than half of their time is spent on compliance programs other than the device GMP program.

[11]We surveyed device GMP inspectors primarily to obtain information on their qualifications. See appendix IV for a description of our survey procedures.

[12]We asked district office management to identify device-qualified inspectors. These were defined as those inspectors they assign to do device GMP inspections. Highly qualified inspectors are those who would be selected first to inspect complex devices.

Classroom courses are offered as well, but only intermittently and not as part of a coordinated training program. We found that 79 percent of "qualified" device GMP inspectors and 49 percent of "highly qualified" inspectors have taken no device-specific training. However, FDA officials that we interviewed said that the agency was starting a medical device curriculum that would include both basic and advanced device courses. In addition to device-specific courses, FDA inspectors take courses such as "New Hire Training," "Evidence Development," and "The Basic FDA Law Course" that apply to all types of inspections.

As a result of both inspection assignment and formal training policies, device inspectors and compliance officers generally cannot acquire and keep up-to-date technical knowledge and skills that are specific to medical devices. One result of this policy is that FDA has only two national device experts, among 329 device-qualified inspectors, who are specialized in particular device technologies. FDA inspectors we interviewed also could identify up to six others who were generally recognized for device expertise.

When device expertise is critical, this cadre of experts can be brought in to serve on inspection teams, but their small number limits this option. However, the use of inspection teams is at the discretion of the district office managers, and according to FDA, most device inspections are performed by individuals.

The Need for More Technical Training

In interviews with FDA and industry experts, we identified several reasons why greater depth of technical knowledge would improve the quality of device inspections and compliance enforcement. On the one hand, technical training is needed to know what production steps are most problematic, which problems are likely to occur in production line tests or in user complaints, and which of these problems are most significant. Training can also improve recognition of failure patterns and when even a small number of failures is significant.

On the other hand, before attention is focused on specific known defects, the current inspection force can easily be confused by the breadth and flexibility of adequacy requirements, making it difficult for them to find the most important among all potential GMP violations. In other words, greater technical training would help inspectors see into complex manufacturing processes and complex devices, and thus help them to know where and how to find the most significant problems.

Furthermore, many current inspectors are at a disadvantage in making a case for compliance enforcement before device users experience serious injury. According to FDA policy, the severity of enforcement action should be proportional to the degree of risk to health and safety that may result from potential device defects. However, without evidence of actual injury and without competence to demonstrate clearly how GMP violations can lead to injuries and deaths, FDA inspectors cannot convince compliance staff that serious GMP violations warrant severe sanctions. Similarly, as former inspectors, district compliance officers are likely to have limited technical knowledge of medical devices, making it even more difficult for inspectors to justify compliance enforcement.

Finally, FDA's recent moves to coordinate device inspections with premarket review of new technology expand the need for technical competence because extensive production line test or user experience data are not available before or soon after new devices are introduced. Thus, a GMP inspector must be able to assess whether process controls and process validation are adequate based mainly on the technical specifications.

Similarly, the need for such coordination and the concomitant demand for technical expertise would increase if FDA implements its proposed inclusion of preproduction quality assurance in GMPs. This is because it makes little sense to inspect for PQA long after users have been exposed to potential design defects in a new device.

The importance of training in device technology was emphasized by the respondents to our survey of FDA's device inspection force. Seventy-five percent of all device inspectors believe that doing more device inspections would be effective in improving their ability to do inspections. Eighty-three percent indicated that FDA device-related courses would be at least moderately effective in improving their ability to do device inspections. Seventy-one percent believe that device-specific technical knowledge is important in doing device inspections, with highly qualified inspectors giving it the greatest emphasis.

In response to these data, FDA officials we interviewed said that device inspectors in the field did not "see the big picture." From this agency perspective, depth of technical knowledge for device inspectors is counterposed to administrative flexibility and breadth in the inspection force to cover the full range of FDA-regulated products.

For example, when grapes from Chile, generic drugs, and HIV (human immunodeficiency virus) contamination of blood banks became national public health concerns recently, FDA was able to rapidly increase the number of appropriate inspections. The agency believes that restrictions against device-specific training contributed to this flexibility. The agency also emphasized that it is difficult to develop and maintain device expertise within each district given its changing mix of food, drug, and device manufacturers.

The scope of our assessment did not permit an evaluation of these administrative constraints on FDA's training policy. However, in interviews with FDA device experts, we found a general concern about the limited technical expertise available to device GMP inspectors. We also found strong interest, among both FDA's device experts and device-qualified inspectors, in expanding the use of inspection teams where technical knowledge could be shared.

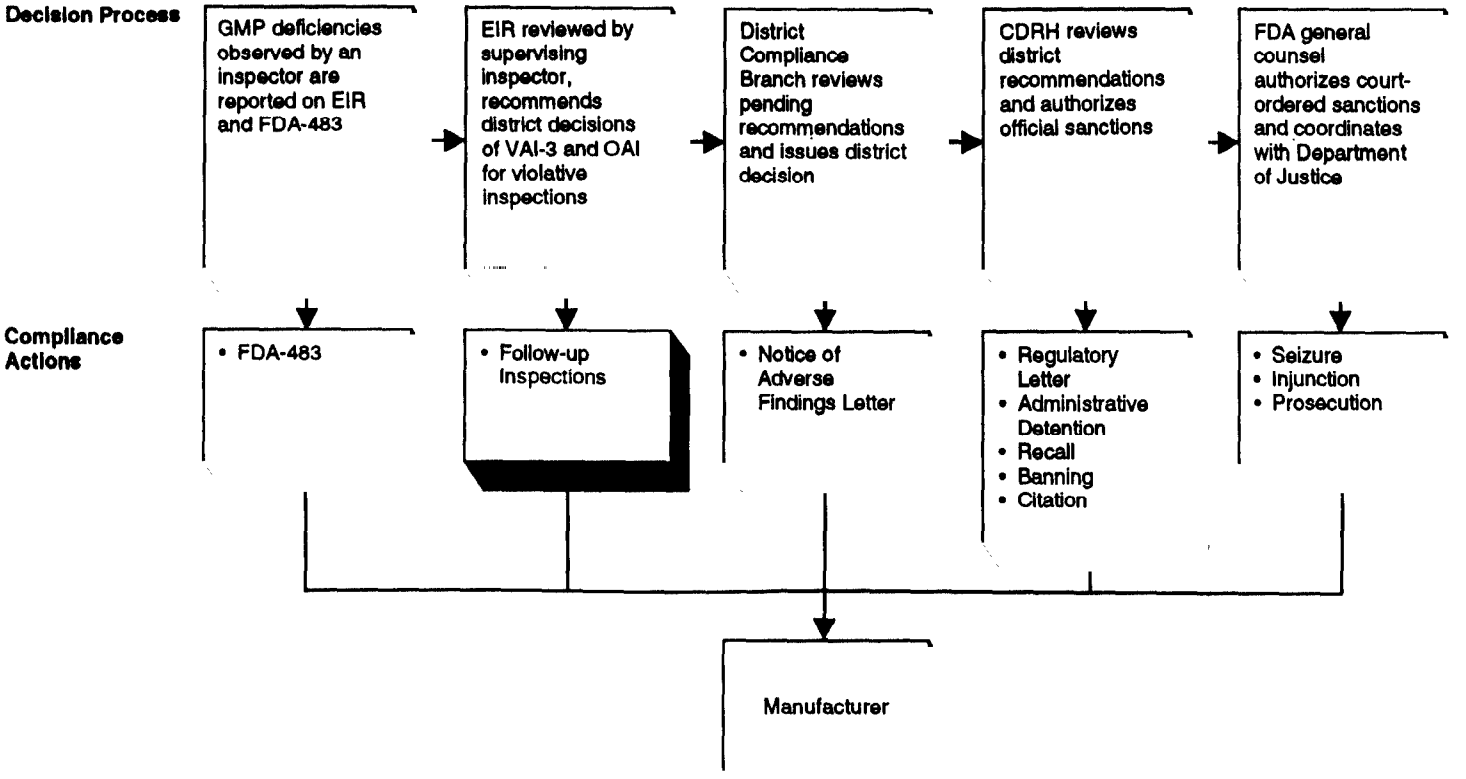
GMP Compliance Process

At the completion of a GMP inspection, the inspector may leave a Notice of Inspectional Observations, or "FDA-483," with the manufacturer. The FDA-483 documents all potential GMP violations observed during the inspection, and it is the manufacturer's first written indication that FDA may take compliance enforcement actions.

Whether or not an FDA-483 was issued, the inspector writes an Establishment Inspection Report (EIR) based upon notes taken during the inspection. If an FDA-483 notice was issued, it is included with the EIR, along with a recommendation to the supervising inspector regarding the form of action needed to bring the manufacturer into compliance. Thus begins a five-step compliance review process as indicated in figure 3.2.[13]

[13]Results from this review process for fiscal years 1987-90, in terms of the number of cases reviewed and actions taken, are presented in figure 4.4.

Figure 3.2: GMP Compliance Review and Enforcement Process



At each step, regulatory discretion is used to balance the severity of compliance enforcement against the significance of GMP violations and the resulting health and safety risks from potential device defects.

The EIR, including the inspector's recommendation for compliance action, is reviewed by the supervising inspector. If the latter concludes that the violations do not warrant regulatory enforcement action, that they have been corrected, or are likely to be corrected by the manufacturer, then the EIR is classified as "no action indicated" (NAI) or "voluntary action

indicated" (VAI-1) and (VAI-2). An NAI conclusion means that no compliance action is required.[14] The VAI conclusions may result in the investigation branch's monitoring the manufacturer to see if it has voluntarily come into GMP compliance.

If the supervising inspector believes that violations listed on the EIR may warrant enforcement action, then the EIR would be forwarded to the district compliance office. When it makes the "district decision," the district compliance office either rejects the EIR as evidence for enforcement action or confirms that such evidence exists and recommends further action to the district management. If the compliance office confirms that enforcement action is warranted, the inspection is classified as a "violative inspection".

The least serious and most frequent violative classification is a third category of "voluntary action indicated" (VAI-3). The most serious GMP violations are classified as "official action indicated" (OAI). According to FDA, district offices are required to report OAI inspections to CDRH for review and approval of recommendations for compliance enforcement action.

The next steps in compliance review and compliance enforcement have recently changed. Before May 1991, if the district compliance office wanted to send a letter to a manufacturer, to document VAI-3 inspections, it could send a Notice of Adverse Findings Letter (NAFL). For OAI inspections, it could submit a recommendation for a Regulatory Letter along with the EIR to the CDRH Office of Compliance and Surveillance. The two letters were similar, except that a Regulatory Letter required a response from the manufacturer within 10 days and it included a warning that if violations were not corrected within this time, administrative or legal proceedings may be initiated.

[14]According to FDA, the terms "deficiency" and "violation" are both used to describe particular objectionable conditions listed by the inspector on the FDA-483 and the EIR. For example, a violation may be failure to document user complaints or inadequate process controls. These particular conditions are to be distinguished from the overall classification of the inspection. According to agency guidance, VAI-1 and VAI-2 inspections are "nonviolative inspections," even though they have uncovered GMP violations. Like NAI inspections, VAI-1 and VAI-2 inspections typically do not lead to compliance enforcement actions.

In May 1991, both Notice of Adverse Findings and Regulatory Letters were replaced by Warning Letters. With certain exceptions, these can be issued without CDRH approval.[15] Like Regulatory Letters, Warning Letters are now the agency's main tool to warn manufacturers that they have GMP violations and that failure to correct them may result in compliance enforcement. They also contain a 15-day response time in which corrections must be made, and they notify the manufacturer that federal contracts will be withheld until corrections are verified. However, Warning Letters do not commit FDA to take compliance enforcement actions if corrections are not made.

If district offices want to initiate compliance enforcement action, they can recommend the following actions to CDRH:

- administrative detention: the temporary removal of a device from domestic distribution for a specified period of time,
- voluntary recall: a negotiated agreement with the manufacturer to recall a device in lieu of official regulatory action,
- banning: elimination of a device from the market,
- citation: a notification of a hearing before the district director prior to a criminal complaint being prosecuted,
- seizure: a court order to remove a device from distribution,
- injunction: a court order prohibiting a manufacturer from producing a specific device,
- criminal prosecution against an individual or corporation.

The last three legal actions must also be reviewed and approved by the FDA General Counsel, which coordinates legal enforcement with the Department of Justice. In May 1991, review procedures prior to injunctions and prosecutions were streamlined by making district, CDRH, and general counsel reviews more concurrent. Data on the frequency of district office recommendations and subsequent FDA approvals are presented in chapter 4.

[15]The initial FDA plan was to replace both NAFLs and Regulatory Letters with only one Warning Letter, but more recent trade press accounts indicate that a second letter may be used in the future for less serious violations. The main exception, where CDRH approval is required before issuing a Warning Letter, involves Medical Device Reporting violations.

Summary

GMP inspections may be a limited (track 1), a comprehensive (track II), or a premarket approval inspection. Premarket approval inspections, for a limited number of class III devices, go beyond track II inspections in scope, and premarket approval depends upon district office certification of GMP compliance.

With the exception of new devices which require premarket approval and a small number of cardiovascular devices subject to a pilot program, class III devices and all class II devices reach the market through the 510(k) or "substantially equivalent" route, without an attempt to coordinate with a GMP inspection. FDA is exploring the feasibility of expanding the 510(k) pilot program to include all class III and critical devices; however, this approach is still a limited substitute for requiring a full premarket approval GMP certification for manufacturers of high-risk devices.

Most device GMP inspectors have academic training in the natural sciences or engineering and many years of on-the-job experience. However, current FDA policy precludes extensive training in device technology for all but a small cadre of experts. According to these experts and current device GMP inspectors, lack of such training limits the inspector's ability to find significant GMP problems and to make a case for compliance enforcement. In contrast to these views, the agency emphasizes administrative constraints that limit the extent of technical training.

When FDA inspectors identify potential GMP violations, they issue an FDA-483 notice to the manufacturer. District offices assess the severity of these violations and then classify each inspection into five broad categories. Only two categories, VAI- 3 and OAI, constitute the more serious GMP violations that warrant compliance enforcement action. Inspections classified OAI involve the most severe violations. Districts are required to report OAI inspections to CDRH for review and approval of recommendations for compliance enforcement.

GMP Inspections and Compliance Actions

FDA collects a variety of data to administer the device GMP program and to monitor the device industry. These data are defined in terms of the GMP requirements, inspection process, and compliance enforcement procedures described in chapters 2 and 3. In this chapter, we examine these data in order to describe and assess the implementation of the GMP program and industry's compliance with the regulation.

This chapter addresses the second objective of this study, to provide a qualitative and statistical review of FDA inspection and compliance actions. To meet this objective, we established the following three questions:

1. How often does FDA inspect device manufacturers?

2. What is the nature and scope of GMP violations?

3. What compliance actions have FDA and device manufacturers taken in response to GMP violations?

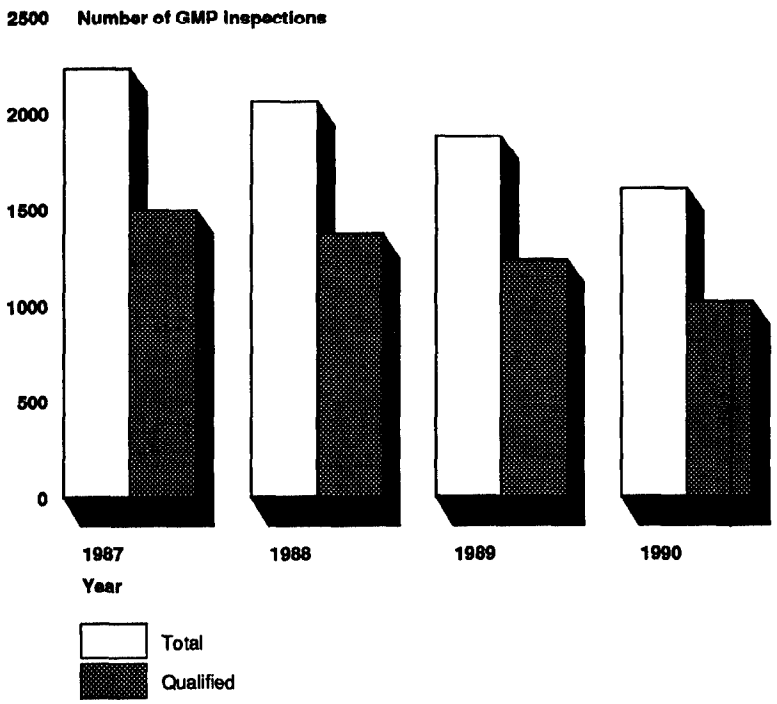
The Frequency of Inspections

The 1976 amendments call for on-site inspection of all medical device manufacturers, and require inspections at least once every 2 years for those making class II and III devices. The latter requirement is commonly called the "statutory obligation." For manufacturers of class II or class III devices, any track I, track II, or premarket approval inspection fulfills or "qualifies" as meeting FDA's obligation.

GMP program data for fiscal years 1987 through 1990 show that a total of 7,764 GMP inspections were conducted, for an average of 1,941 each year. Out of this total, 5,112 (66 percent) qualified as meeting the statutory obligation for class II or III devices; the rest were inspections of class I devices or follow-up inspections.[1] About 39 percent of these qualifying inspections were track I inspections, 58 percent were track II inspections, and 3 percent were premarket inspections. As shown in figure 4.1, during fiscal years 1987-90, there was a steady decline both in the total number of device GMP inspections and in the number of qualified inspections.

[1]Follow-up inspections are conducted to check whether GMP deficiencies noted during previous track I or II inspections have been corrected. If that is all they do, they are counted as follow-up GMP inspections in the annual total of GMP inspections. However, sometimes follow-up inspections are combined with track I or II inspections, and these would be counted in the annual totals as qualifying inspections.

Figure 4.1: GMP Inspections for Fiscal Years 1987-90



Domestic Device Manufacturers

Domestic device manufacturers of all class II and III devices and some class I devices are required annually to register the sites where they manufacture devices and to list the devices they manufacture. Based on inspection records and on these registration and listing data, FDA estimates that there are currently between 4,000 and 5,500 domestic manufacturers of class II and III devices.[2] Using the lower boundary, 1,650 class II or III manufacturers (41 percent) have not been inspected within the past 2 years. Using the upper boundary, about 57 percent of these manufacturers would not have been inspected on time. Therefore, even under the most conservative circumstances, our analysis indicates that the quality assurance systems of over 40 percent of domestic manufacturers of class II and III devices have not been reviewed for at least 2 years.[3] Furthermore, the declining trend in the number of qualified inspections means that the

[2]These two FDA numbers define the current range of uncertainty. They were obtained from the Office of Regulatory Affairs and CDRH, respectively. See discussion of FDA data systems below for further explanation of this uncertainty.

[3]According to FDA officials, the agency does not have an accurate inventory of nonexempt class I manufacturers and, therefore, cannot document how often they were inspected.

situation is worsening. Twenty-five percent or less of all class II and III manufacturers were inspected last year.

Foreign Device Manufacturers

FDA estimates that there are at least 1,450 foreign manufacturers that market class II and III devices in the United States. The agency cannot require them to have on-site inspections; however, GMP inspections are routinely conducted abroad, by FDA, through memorandums-of-understanding between the agency and its counterpart in the exporting country and through the voluntary cooperation of manufacturers.[4] Unlike domestic manufacturers, foreign device manufacturers are given prior notice of an inspection so they can give permission to conduct one.

Our analysis of FDA records of foreign GMP inspections during recent years shows that only about 175 manufacturers (12 percent of these exporting to the United States) have been inspected in a year. At this rate, foreign manufacturers are inspected about once every 8 years—four times less frequently than is required for domestic device manufacturers.

Do GMP Inspections Identify Defective Devices Before Manufacturers Initiate Recalls?

Like premarket review, the primary objective of the GMP regulation is to prevent defective devices from reaching the market. However, since not all defects can be prevented before marketing, a critical secondary objective for the GMP program is to identify defective devices as soon as possible in order to minimize risk exposure to users. The latter is similar to the objective of the postmarketing surveillance program—to give an early warning of injuries and deaths related to defective devices in order to remove such devices from the market as soon as possible.

Medical device recalls constitute one element of FDA's postmarketing surveillance system.[5] If a device exhibits a problem after it has been made available for general use, or if data on users' experience (from FDA's Medical Device Reporting Program as well as other sources) indicate that a

[4]FDA has some authority over foreign device manufacturers of new class III devices that have premarket approval requirements, because these devices cannot be marketed in the United States without an FDA inspection. According to FDA, all other class III and all class II devices made abroad can be marketed here as long as the manufacturer lists the device with FDA, submits a 510(k) for devices introduced in 1976 or after, and the device does not appear to be adulterated or misbranded.

[5]See Medical Device Recalls: An Overview and Analysis 1983-88, GAO/PEMD-89-15BR (Washington, D.C.: Aug. 30, 1989) for further background on device recalls. The Safe Medical Devices Act of 1990 authorized FDA to initiate recalls and it required manufacturers to notify FDA when they recall a device. Before enactment of the Safe Medical Devices Act, the agency had limited authority to order manufacturers to repair, replace, or refund the purchase price of devices that present an unreasonable risk of substantial harm to the public health.

problem's rate of occurrence exceeds an expected range, one of the remedial actions available to FDA and to the device's manufacturer is to recall the product or remove it from the market.[6]

GMP inspections may provide an alternative signal to initiate a recall, before device users report problems, if inspections occur during the time when defective devices are made and if they also uncover related quality assurance problems. We used GMP inspection records, in conjunction with recall data, in order to assess whether GMP inspections could have given such a signal. We focused primarily on class 1 and 2 recalls because they involve the most seriously defective devices that could cause death or injury.[7]

We examined the targeting and the effectiveness of inspections for 751 recalls that were initiated by domestic manufacturers in the 4 fiscal years from 1987 through 1990.[8] Out of these 751 recalls, we focused primarily on a subset of 493 class 1 or class 2 recalls initiated by 322 manufacturers.

Regarding the targeting of GMP inspections, we focused on the first recall for these 322 manufacturers. The first recall is important to assess the timeliness of routine inspections or inspections not targeted on the basis of an earlier recall. We also used the interval of 2 years as the appropriate time interval between inspections, based upon the statutory obligation. Thus, we assumed that if an inspection occurred within 2 years before a recall, it had a better chance of triggering a recall than if the time interval exceeded 2 years.

We found that 34 percent had no inspection in the 2 years before their first recall.[9] In other words, for about a third of manufacturers with device recalls, GMP inspections had little chance of either initiating recalls (or preventing them by preventing the manufacture of defective devices) because they did not occur in time.

[6]See Medical Devices: FDA's Implementation of the Medical Device Reporting Regulation, GAO/PEMD-89-10 (Washington, D.C.: Feb. 17, 1989) for a description of user experience reporting via the medical device reporting system.

[7]As discussed in chapter 1 of this report, the 1976 amendments created a three-tiered system in which devices would be classified in ascending order according to their potential risk, with class I devices presenting the least risk and class III devices the most. FDA classifies the potential health risk associated with recall classes in descending order, with class 1 recalls presenting the greatest risk and class 3 the least. See Medical Device Recalls: Examination of Selected Cases, GAO/PEMD- 90-6 (Washington, D.C.: Oct. 19, 1989), appendix III, for a discussion of recall classification.

[8]An additional 124 recalls may have occurred during this 4-year period, but they were not included in this analysis because the exact date of recall initiation was not reported in FDA's file.

[9]We obtained similar results when the 258 class 3 recalls were included in the analysis.

Regarding the effectiveness of GMP inspections, in finding manufacturing problems before recalls, we examined only those recalls out of the 493 cases that were caused by manufacturing problems. Many recalls are caused by defects in device design, but we focused only on manufacturing problems since that is the focus of current GMP inspections. There were 220 such recalls that were preceded within 2 years by a GMP inspection. Twenty-seven percent of these inspections found no GMP violations, and another 46 percent had violations that did not warrant compliance enforcement. This means that a total of 73 percent of these inspections found no serious GMP violations. Since these recalls involved defective devices that could have serious health consequences, this result indicates that FDA frequently did not find GMP problems before they caused defects that placed device users at risk.

There are several possible reasons why GMP inspections did not find the manufacturing problems that eventually caused recalls, including the level of inspector competence, the possible deterioration of manufacturing practices after an inspection occurred, or events such as a key technician's illness or conflicts among staff within a plant that may not be entirely controllable by quality assurance systems. Other explanations include the use of track I (limited) and profile class inspections that do not cover all GMPs and all manufacturing processes.

The available data do not reveal which of these reasons explain why GMP inspections may have failed to find GMP violations that eventually led to recalls. They also do not identify how many device defects and device recalls may have been prevented by FDA inspections and FDA enforcement of GMP compliance. Consequently, we cannot make an overall assessment of GMP program effectiveness. On the other hand, it is important to note that FDA does not report data that would indicate when GMP inspections led to recalls.[10] Such data would help to demonstrate when GMP inspections did trigger recalls of defective devices and thus reduced public exposure to health and safety risks.

[10]As the agency's eyes and ears, district offices track manufacturer and FDA actions following violative inspections, and so, they know when inspections led to recalls.

Recent Patterns in GMP Violations and Deficiencies

During fiscal years 1987-90, 4,259 FDA-483s were issued by inspectors as a result of 7,764 device GMP inspections.[11] That is, 55 percent of these GMP inspections uncovered potential GMP violations, and on an annual basis, the rate of FDA-483s issued increased slightly over the period. According to official guidance, district offices should report all FDA-483s to CDRH; however, we found that about 36 percent were not reported and that FDA has not sampled these missing cases to establish whether they are different from reported cases.[12] Nevertheless, according to FDA, the reported sample of cases is sufficient to monitor patterns in GMP violations and deficiencies.

We examined the violations and deficiencies listed on FDA-483s for domestic manufacturers.[13] We examined them separately for critical and noncritical devices, focusing mainly on critical devices since they present the greatest health risks. We also aggregated over 169 specific violation codes into 15 types or categories, using FDA's classification system.[14] During fiscal years 1987-90, the average FDA-483 issued to a manufacturer of critical devices contained 4.4 different types of violations and deficiencies in 1987, 5.2 in 1988, 5.5 in 1989, and 5.0 in 1990. Manufacturers of noncritical devices had slightly fewer of these items per FDA-483, with 4.2 in 1987 and 1988, 4.8 in 1989, and 4.7 in 1990.

We also examined the relative frequency pattern among these 15 categories and how they changed over time. Figure 4.2 shows that relative frequencies did not change significantly over time.

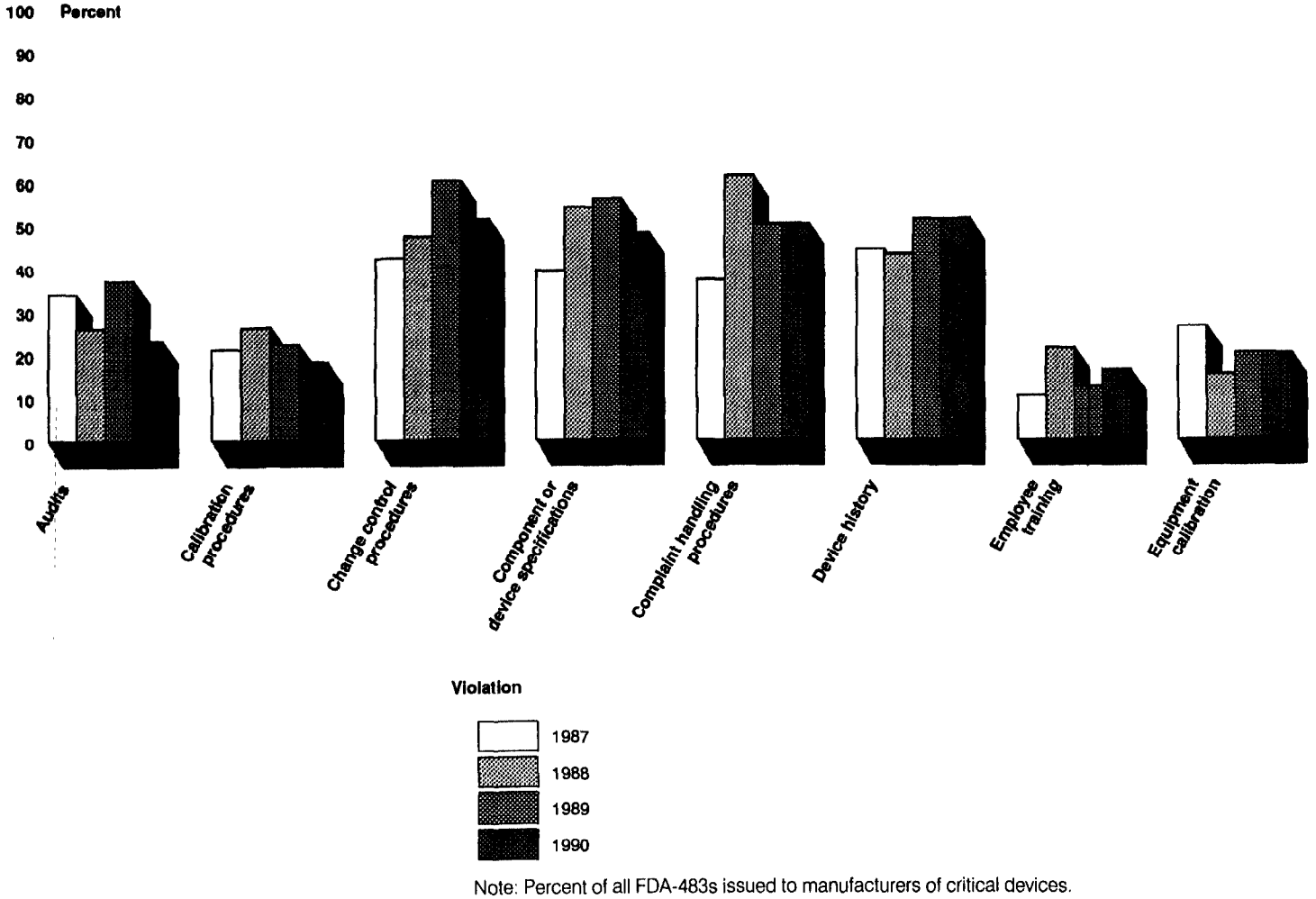
[11]FDA reports GMP inspection results in two different central files, the Program Oriented Data System and the FDA-483 file for inspections that result in an FDA-483 notice. The total number of FDA-483s issued and district office decisions about their significance were calculated using both files.

[12]The agency can identify all FDA-483s and could sample from the population of unreported FDA-483s to validate whether reported cases are representative.

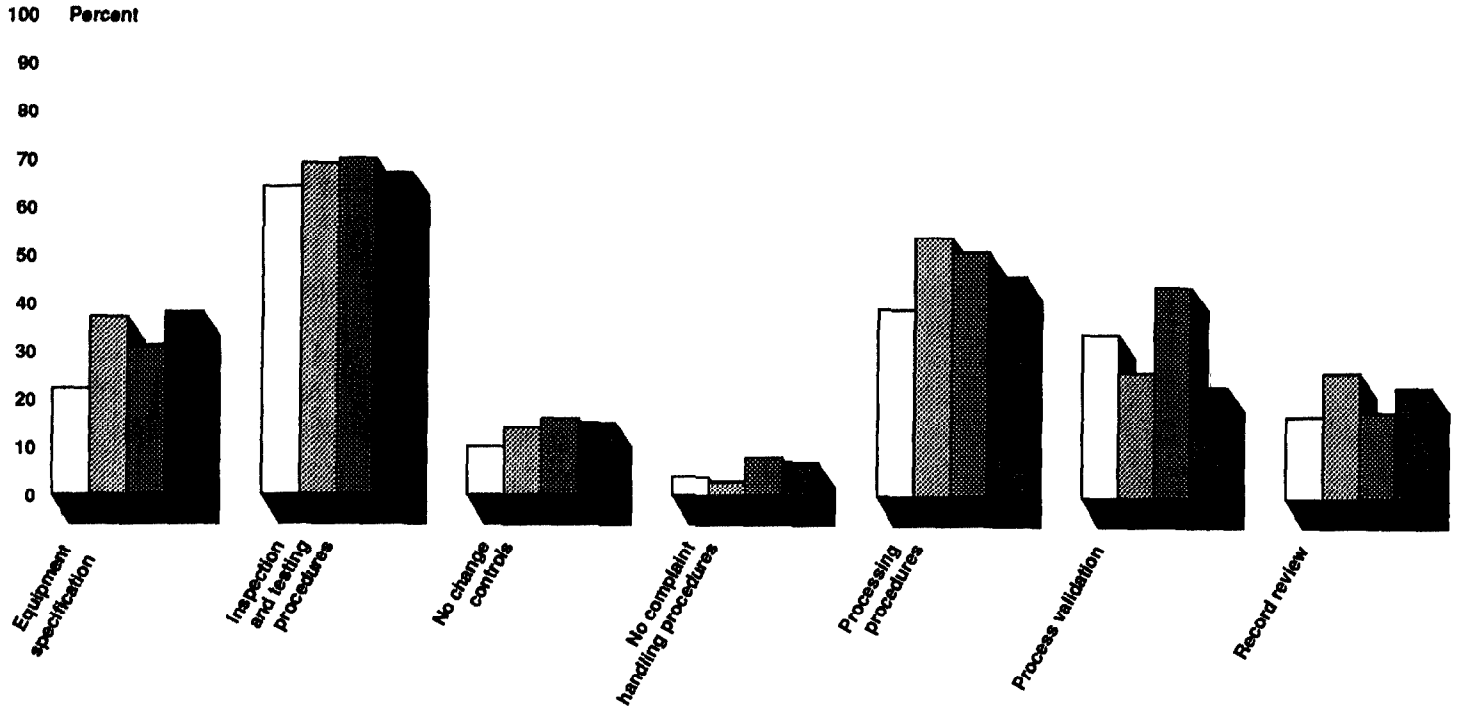
[13]We did not consider FDA-483s reported from foreign inspections because the information reported for these cases was often incomplete. There were 3,979 FDA-483s issued to domestic manufacturers during this 4-year period and 2,465 (62 percent) were reported to CDRH.

[14]These categories were defined by FDA as: quality assurance system audits; written calibration procedures; change control procedures; use of controls in making changes; specifications for components or finished devices; complaint handling procedures; device history records; equipment calibration; equipment and maintenance specifications; inspection and testing procedures for determining specification conformance; absence of complaint handling procedures; processing procedures; process validation and equipment qualification; record review of in-process or finished devices; documentation of employee training. See appendix V for definitions.

Figure 4.2: GMP Violations and Deficiencies for Manufacturers of Critical Devices, by Problem Category



Note: Percent of all FDA-483s issued to manufacturers of critical devices.


100
Percent
90
80
70
60
50
40
30
20
10
0
Equipment specification
Inspection and testing procedures
No change controls
No complaint handling procedures
Processing procedures
Process validation
Record review

During all 4 years, the most frequently cited GMP problem involved device inspection and testing procedures employed during and immediately after the manufacturing process. The purpose of inspection and testing is to identify devices that do not perform to design specifications, for whatever reason, before they are shipped to users. However, an FDA official commented that the high frequency of this GMP problem may not indicate that this is the worst problem because inspectors have relatively good training in inspection and testing techniques, and thus may focus more attention on what they know best.

Other frequent problems are change control, complaint procedures, component and device specifications, device history records, and processing procedures. The importance of change control and FDA's expansion of change control requirements were discussed in chapter 2, as was failure investigation, a key element of complaint handling procedures.

Deficient component and device specifications may lead to defective devices if, for example, written specifications do not exist or are not properly used to select or reject items for device assembly or shipping. Device history records track the components used and the production test results for each lot or production run. Deficient history records may prevent a verification that appropriate components were used and tests were run. Finally, deficient processing procedures may lead to defective devices directly, by producing devices that do not meet specifications. This often cannot be identified except by process validation. (See chapter 2.)

Our analysis of violations and deficiencies for noncritical devices revealed a similar pattern among GMP problem categories, although noncritical devices had a higher relative frequency of device history record and quality assurance system audit problems. Audits are periodic reviews of all quality assurance activities to assess whether they work together to ensure a quality final product. Based upon the available data and interviews with FDA officials, we could not interpret whether these differences between critical and noncritical devices were significant.

In addition to describing these relative frequencies, the data reported from FDA-483s have recently been used by FDA to identify GMP violations, by device type, that resulted in regulatory actions.[15] Data reported on FDA-483s also permit a limited analysis of industry response to FDA inspection experience, which we discuss below.

[15]In October 1991, this information was provided as guidance to district offices to help identify the most important GMP violations.

FDA's Response to GMP Violations

District Assessment of Inspection Results

When an inspector finds potential GMP violations and issues an FDA-483 notice, the district office assesses their overall severity by classifying the inspection (in order) as official action indicated (OAI), voluntary action indicated (VAI-3, -2, -1) and no action indicated (NAI). Our compilation of these district decisions, for fiscal years 1987-90, is presented in table 4.1.

Table 4.1: District Office Decisions for FDA-483 Notices

		Percent of all	
Decision	**Number**	**FDA-483 notices**	**Inspections**
OAI	482	11	6
VAI-3	763	18	10
VAI-2 and VAI-1	2,237	53	29
NAI	566	13	7
Pending	187	4	2
None reported	24	1	0
Total	**4,259**	**100**	**54[a]**

[a]About 45 percent of inspections do not result in an FDA-483 notice.

Note that the frequency of these inspections is reported in table 4.1 as a percentage of all FDA-483s issued and as a percentage of all inspections. The latter is smaller because about 45 percent of inspections do not result in an FDA-483 notice.According to FDA policy, only inspections classified as OAI and VAI-3 are violative inspections, and thus only these cases typically result in an FDA compliance action. Furthermore, only inspections classified as OAI involve sufficiently serious violations that district offices have been required to report inspection results and their recommendations for regulatory action to compliance reviewers at CDRH and to a special data base at FDA headquarters.

Central FDA Review and Reporting of Serious GMP Violations

FDA has two central data filing systems to track OAI cases, including the district office recommendation for compliance action and whether it was approved by CDRH or higher FDA authority. (Neither data system monitors compliance actions taken by district offices to correct violations of the regulation that do not require CDRH approval.) The first is the Regulatory Actions Control System (RACS), an automated central file maintained by the

Office of Regulatory Affairs, which includes device cases along with drug, food, and other FDA regulatory targets. District offices are required to enter cases into this system and report their recommendations for compliance action for all OAI inspections.

The second data system is composed of two files, one automated and the other a hard-copy log. This system is maintained by CDRH, Division of Compliance Operations, to monitor compliance enforcement only for medical devices. It contains all district office recommendations for compliance action that have been submitted to CDRH for approval. However, since the automated file only contains summary information from district recommendations for compliance enforcement, data on approved compliance enforcement actions can only be obtained from hard copy.[16]

We attempted to use both systems to track the disposition of the 482 OAI recommendations—that is, FDA-483 notices on which official action was indicated. (See table 4.1.) However, because of the fragmented nature of the available data bases and the amount of critical information that is missing, we can only estimate the set of compliance recommendations related to inspections in fiscal years 1987-90.

In the RACS system, we were able to identify only about 188 of the 482 OAI cases (39 percent).[17] Furthermore, 66 of these 188 cases (35 percent) did not include information about CDRH approval or disapproval or final FDA actions. As a result of these missing cases and missing data, RACS can account for the disposition of only about 26 percent of the 482 OAI cases. This low rate of reporting of complete information meant that we could not use this file as a source of information.

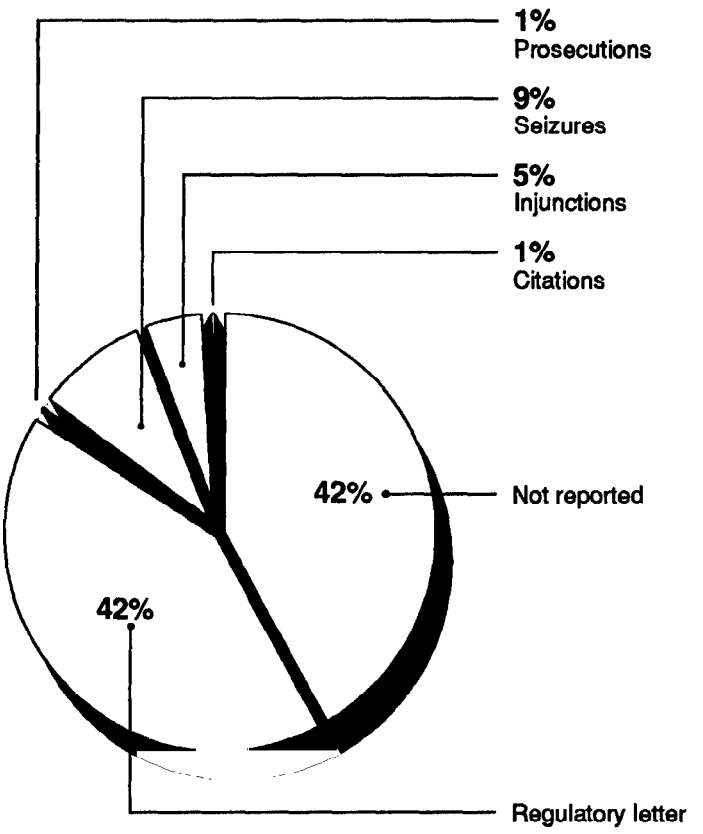
In the dual file system maintained by CDRH, an estimated 278 district office recommendations for GMP-related compliance enforcement action

[16]The automated data system has been operating for the last 5 years; however, CDRH staff in charge of handling the approval process rely only on hard copy files because they consider the automated system unreliable.

[17]Although this system uses a numeric code to identify manufacturers, it does not contain a unique identifier to link specific inspection results to compliance actions. A rough association can be made, however, by comparing the date of inspection to the date when a district submits a recommendation for approval to CDRH.

(58 percent) could be associated with the 482 OAI inspections during fiscal years 1987-90.[18] As a possible explanation for the large number of OAI cases not reported to CDRH, FDA officials indicated that the agency had discouraged the issuance of regulatory letters and more severe sanctions during the 1980s by advising district offices to negotiate voluntary corrections whenever possible. CDRH data are presented in figure 4.3.

Figure 4.3: District Office Recommendations for CDRH Approval of Compliance Actions



Note: Number equals 482.

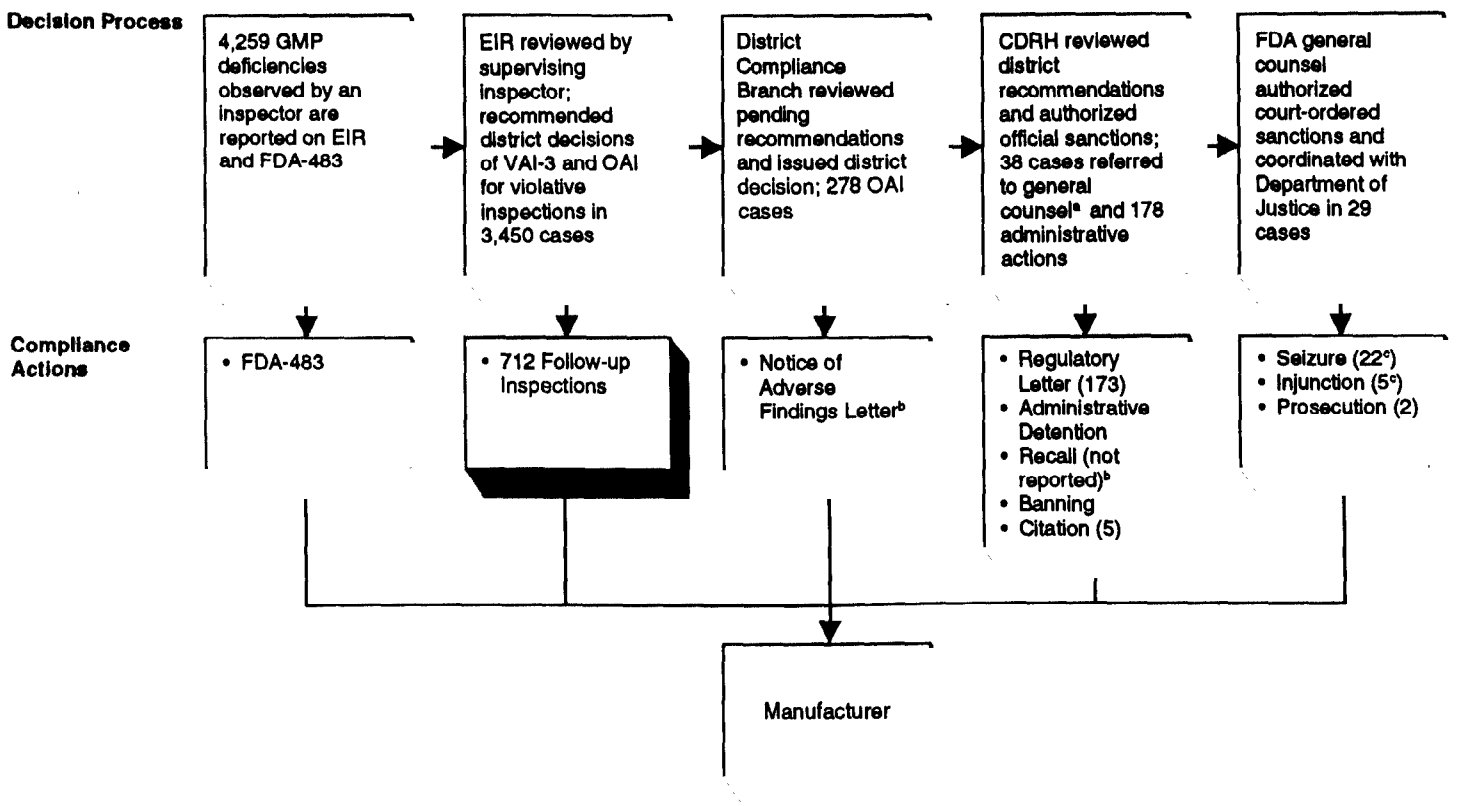
Among the 278 reported district office recommendations for compliance enforcement, Regulatory Letters were by far the most frequent. Seizures were next, followed by injunctions, citations, and prosecutions. This

[18]We identified CDRH cases manually, assuming that they were associated with OAI inspections during fiscal years 1987-90 if they were reported during the same 4 fiscal years or during the last 3 months of 1990. The last 3 months were included to allow for time to process inspection cases toward the end of fiscal year 1990.

pattern reflects a "funneling down" in numbers in inverse proportion to the severity of enforcement action. The least severe actions were recommended most often, and vice versa.

The disposition of these 278 cases is presented in figure 4.4. To link the information presented in figures 4.3 and 4.4, notice that the 58 percent of OAI cases reported to CDRH (figure 4.3) equals (with rounding errors) the 278 cases reviewed in step 4 of figure 4.4.

Figure 4.4: Device GMP Compliance Actions (Fiscal Years 1987-90)



[a]Includes four recent cases (one injunction and three seizures) that are still pending.

[b]Numbers not reported.

[c]Includes cases where legal action was approved but did not result in a court proceeding because the threat was sufficient to motivate voluntary compliance.

Among the 278 district office recommendations to CDRH, 208 were approved (74 percent), including 170 administrative actions (i.e., 165 regulatory letters and 5 citations) and 38 legal actions (2 prosecutions, 7 injunctions, and 29 seizures). Among 68 district office recommendations for legal action, CDRH approve 2 out of 3 prosecutions, 7 out of 22 injunctions, and 29 out of 43 seizures, for an overall approval rate of 56 percent. Eight recommendations for legal action were downgraded by CDRH and approved as regulatory letters, making a total of 173 regulatory letters issued.

The 38 CDRH-approved legal actions must also be approved by the FDA general counsel. The latter approved 29 cases, with 5 recent cases still under review. Excluding the 5 recent cases, 46 percent of district recommendations for legal action were ultimately approved by both CDRH and the FDA general counsel.

In addition to the preceding analysis of FDA data, we surveyed device inspectors for their opinions about the appropriateness of compliance enforcement, and we also reviewed case studies of medical device problems involving GMP problems. Our survey found that most device inspectors believe that noncompliance with the GMP regulation could be reduced if enforcement sanctions were more certain and more severe. Furthermore, two case studies document recent instances when the identification of serious device defects by district offices did not immediately lead FDA to take compliance enforcement actions sufficient to correct GMP problems.[19] Regarding the appropriateness of compliance enforcement for device GMPs, FDA has not had an independent review of its enforcement actions.

Manufacturers' Response to GMP Violations

As discussed in chapter 1, one of the four major factors underlying the effectiveness of the GMP program is the response of the medical device industry once GMP violations have been identified. For fiscal years 1987-90, we examined pertinent information reported from 2,460 domestic inspections that resulted in the issuance of FDA-483s.[20] About 87 percent of

[19]For a discussion of the Bjork-Shiley Heart Valve, see Committee Print 101-R, House Committee on Energy and Commerce, Subcommittee on Oversight and Investigations. For a discussion of the Aequitron apnea monitor, see our report entitled Underreporting of Serious Problems With a Home Apnea Monitor, GAO/PEMD-90-17 (May 31, 1990).

[20]As discussed earlier in this chapter, reported FDA-483s include pertinent information for 2,465 out of the 3,979 domestic inspections that resulted in an FDA-483 notice during fiscal years 1987-90. We did not consider FDA-483s reported from foreign inspections because the information reported for these cases was often incomplete.

inspections in this sample involved manufacturers of noncritical devices. The remaining 13 percent involved manufacturers of critical devices.

We first grouped these FDA-483 notices according to whether or not the inspection was the first for the manufacturer. Twenty-four percent of inspections for manufacturers of noncritical devices and 13 percent of inspections for manufacturers of critical devices were initial inspections.

For manufacturers of noncritical devices, our analysis showed that 34 percent of the FDA-483s issued on initial inspections (during fiscal years 1987 through 1990) were violative. That is, they warranted compliance enforcement action. About the same percentage of subsequent inspections were violative. Manufacturers of critical devices actually had a lower percentage of violative FDA-483s on initial than on subsequent inspections, 32 percent versus 45 percent. The data do not indicate whether violations found during initial inspections were the same or different than on subsequent inspections, but these comparisons nonetheless suggest that experience with GMP regulation did not improve GMP compliance.

Next, we examined the 44 percent of cases in this sample that involved manufacturers who received two or more FDA-483s in succession. About half of these manufacturers (of both critical and noncritical devices) did not correct GMP violations from one inspection to the next.

Finally, we examined data concerning the rate of violative inspections for manufacturers who had manufacturing-related recalls during the 2 years prior to the issuance of the FDA-483. These data do not indicate whether the GMP problem that caused each recall is similar to the violations reported on subsequent FDA-483s, but they nonetheless help to assess manufacturers' response to GMP problems because such recalls should be a clear signal that manufacturing quality assurance procedures need improvement.

Seven percent of noncritical device manufacturers in this sample and 23 percent of manufacturers of critical devices had such recalls. About half of noncritical device manufacturers had a violative inspection following the recall. A smaller percentage of critical device manufacturers in our sample had violative inspections following a recall, but these still occurred more often than the average for all GMP inspections.

All three of these situations show that, overall, manufacturers have not improved their rate of compliance with the GMP regulation. Although we

cannot determine whether the problems are the same or new, we can say that GMP problems have tended to persist over time.

FDA Data Systems

Over the last 12 years, FDA has developed several automated data systems to monitor GMP program data, including the inventory of manufacturers, inspection activities and results, FDA-483 notices of potential GMP violations, compliance enforcement actions, and device recalls. The Office of Compliance and Surveillance within CDRH has used these data, particularly recall data, to upgrade device GMP requirements. However, in using these data systems to describe and assess the GMP program, we identified a number of gaps and other limitations.

Manufacturer and Device Inventories

FDA identifies device manufacturers who should be inspected when manufacturers comply with the requirement that they register their manufacturing sites with FDA each year and list the medical devices manufactured at each site. However, we found that these computer files are not validated to verify their accuracy, and the data are not archived for historical analysis.[21] Consequently, FDA does not know the number or location of all domestic device manufacturing sites that are subject to biennial GMP inspections, nor can the agency document how the inventory of manufacturers and manufacturing sites has changed over time. The inventory of foreign manufacturers of class II and III devices is less accurate still.

FDA also does not attempt to estimate the inventory of devices marketed or in use. While this is not required by law, such an inventory is critical for assessing the relative importance of GMP problems and their consequences in terms of device recalls and device-related injuries and deaths. Information about the latter may come not only from Medical Device Reports that manufacturers currently must submit to FDA, but also from user facility reporting of all device-related injuries and deaths recently mandated by the Safe Medical Devices Act.[22]

[21]Problems with FDA's registration and listing data were previously reported by GAO, and that raises the question of why FDA has not corrected the situation. (See FDA's Implementation of the Medical Device Reporting Regulation, GAO/PEMD-89-10 (Feb. 17, 1989), p. 51.) According to FDA, steps have been taken very recently to improve registry and listing data. These include a major upgrade to the device coding system, to make it easier for manufacturers to identify and classify their devices, and an integration of the registration and listing processes. We could not assess these improvements because they were implemented in the late summer of 1991, after the data-gathering phase of this project.

[22]See FDA's Implementation of the Medical Device Reporting Regulation, GAO/PEMD-89-10 (Feb. 17, 1989) for further background on medical device reports.

Furthermore, at least until the recent upgrade, FDA's device classification system did not facilitate description of the device inventory because its product codes had not been systematically updated since they were originally published in 1977 and because they did not adequately distinguish devices by type and by use.[23] Even with the recent upgrade, FDA's device codes are difficult to use because they were generated using a random letter generator. Consequently, there is no similarity of codes among similar devices and there is no way to search for a particular device the way one might search for a library book using the Dewey decimal system. Another indication of problems with FDA's device classification is that, for the last 5 years, FDA's main computer file for inspection results has not used device codes to report devices manufactured at the site being inspected. Consequently, FDA cannot use inspections to routinely confirm whether manufacturers make the devices that they have listed with the agency.

Reporting Inspection Results

FDA's central file for reporting inspection activities and results reports only minimal inspection results. Specifically, it does not group inspections that are made to track a specific compliance problem and it does not indicate when a GMP inspection led to a recall. Because these data are missing, it is difficult to use this file to document when inspections effectively tracked and corrected GMP problems.

Reporting of violations and deficiencies listed on FDA-483s is incomplete as discussed above. Thirty-six percent of FDA-483s are not reported. In addition, this central file lists all GMP violations and deficiencies listed on FDA-483 notices but does not identify which GMP violations are most significant; that is, which involve the greatest safety and effectiveness risks. Like the information about whether an inspection led to a recall, this information is available to district offices. If reported, it could be compared to the cause of any subsequent recall in order to assess whether the inspection effectively uncovered the recall problem. An inspection might also identify a GMP problem but not clearly enough to justify a recall. If a recall subsequently happens, nevertheless, it would raise a question about FDA's assessment of inspection results.

[23]Institute of Medicine, The NLM and Health Care Technology Assessment: Improving Information, Appendix F (Washington, D.C.: 1989). We did not assess FDA's recent upgrade of its device classification system because it was published after the data-gathering phase of this project.

Reporting Compliance Actions

FDA maintains two central filing systems for tracking compliance enforcement recommendations and actions, but as indicated above, neither provides a complete accounting of OAI cases that should be reported. Furthermore, neither system monitors compliance actions taken by district offices to correct violations of the regulation (those inspections rated VAI-3) that do not require CDRH approval. The latter violations occur much more often than the violations that must be reported, and so they may account for many more unreported compliance actions. All of these missing cases limit nationwide monitoring and assessment of compliance enforcement. The problems of missing cases and missing data are particularly severe for the FDA-wide RACS system, raising the question whether it is worth maintaining in its present form.

Data Hardware and Software Systems

We found several examples of obsolete and incompatible computer technology. Obsolete technology includes data base software and the absence of area networks, which hinder attempts to identify, access, and analyze relevant data sets. Incompatible hardware and software are often maintained by different units within FDA, making automated transmission of data impossible without labor-intensive programming efforts. Furthermore, we found that little has been done to organize and store data files to facilitate description of program activities over time. All of these data system problems make it unnecessarily difficult to use FDA data to broadly assess GMP program operations.

The New Field Information System

According to FDA officials, many problems of missing data and obsolete and incompatible computer systems will be solved by the new Field Information System (FIS) that is currently being developed and deployed. This new system, for which about $10 million has been committed out of an estimated total cost of $25 million, would permit data entry on site, during inspections, using laptop and notebook computers. It would also provide high-speed data transmission links between district offices and FDA headquarters, with compatible hardware and software throughout the system. All of these improvements could make it much easier and less expensive to enter critical data into the automated system and to identify and retrieve data from any location no matter what FDA unit maintains the file.

This new FIS system could greatly increase the number of empirical questions about the GMP program that can be answered. However, it is still too early to tell whether system design and data storage capacity as well as the

definition of data and data files will actually do more than support narrowly defined program operations.

Summary

The total number of GMP inspections and inspections for class II and III devices have both declined steadily during fiscal years 1987-90. As a result, at least 40 percent of manufacturers have not been inspected on time. Less than 25 percent of the domestic inventory was inspected last year. Foreign importers were inspected much less often.

We found that infrequent inspections limited the effectiveness of GMP inspections either to prevent device defects or to initiate recalls of defective devices before recalls are triggered by users' experience. For manufacturers who recalled seriously defective devices, about a third had not had an inspection within the 2 years preceding their first recall. Furthermore, when inspections did occur within the preceding 2 years, seriously defective devices were often recalled by manufacturers because of GMP violations, despite the fact that the manufacturer was found to be in compliance with GMPs.

During fiscal years 1987-90, about 55 percent of GMP inspections resulted in an FDA-483 notice issued to the manufacturer. Annually, this percentage increased slightly over the period. For manufacturers of critical devices, we found that the number of different types of violations and deficiencies per manufacturer has not declined over time, nor has the relative frequency of different violations changed significantly. These patterns for noncritical devices were similar.

Over the same period, most FDA-483s did not involve serious violations of the GMP regulation. Together with inspections where no FDA-483 was issued, 84 percent of all inspections found no violations that warranted compliance enforcement action. The most serious GMP violations should be reported both to CDRH, for approval of compliance enforcement actions, and to a central FDA file that monitors compliance enforcement actions. A large percentage of these cases are missing from both files. Of the cases submitted to CDRH for approval, most district recommendations for enforcement action were approved.

Regarding the appropriateness of FDA compliance enforcement actions, we found that FDA inspectors generally believe that stronger enforcement could reduce noncompliance. We also found cases where identification of seriously defective devices by district offices did not immediately lead to

severe sanctions. FDA data also suggest that industry experience with GMP regulation over recent years has not improved the rate of compliance and that GMP problems tend to persist.

Finally, we found that FDA device program data are of limited use in describing the GMP program and its effectiveness. Because FDA does not accurately estimate the inventory of manufacturers, and does not attempt to estimate the inventory of medical devices, the significance of GMP problems and related device recalls and device defects cannot be assessed by comparing their numbers to the total number of manufacturers and the total number of devices.

In addition to the failure of districts to report many of the most serious violations of the regulation and many compliance enforcement actions, we identified important data resident in district offices but not reported in any central FDA file. According to FDA, many of these reporting problems as well as computer system problems may be solved when the agency completes deployment of a new Field Information System.

Conclusions, Recommendations, Agency Comments, and Our Response

The focus of our review was the structure and implementation of FDA's Good Manufacturing Practices (GMP) regulation. We pursued two study objectives, which were to (1) develop an analytical description of the program that FDA has established to promote quality assurance in device manufacturing, and (2) provide a qualitative and statistical review of FDA's inspection and compliance actions.

We address these objectives in terms of four factors that determine industry compliance with GMPs: (1) the extent of agreement that FDA's GMPs are reasonable quality assurance standards for manufacturing; (2) the targeting of inspections to manufacturers with potential problems; (3) the technical competency of FDA inspectors to distinguish good manufacturing practices from manufacturing problems; and (4) the response of FDA and manufacturers to correct manufacturing problems after they have been identified by inspectors. This chapter draws conclusions about the status of these factors and how they strengthen or weaken the GMP program.

Conclusions

GMP Requirements

In the 1978 regulation, FDA defined good manufacturing practices broadly in terms of quality assurance objectives that applied to all medical devices. However, their application by FDA inspectors and compliance officers was specific to each device, in proportion to the potential for errors in manufacturing and the resulting risk of injury or death.

These quality assurance objectives employ two performance criteria, one more stringent than the other. The less stringent criterion requires that manufacturers have a written quality assurance plan and that they adhere to it. The more stringent criterion can be much more difficult to translate into operational inspection guidelines because it requires manufacturers to meet industry standards. The two criteria are different, in practice, only if FDA inspectors are sufficiently competent and experienced in device and manufacturing technology to recognize the existence of industry standards and then to assess whether specific device manufacturers meet these standards.

Based mainly upon its experience with device recalls, FDA has expanded its interpretation of the 1978 regulation over time, using more stringent criteria in an attempt to reduce health and safety risks. We generally agree with FDA's definition of GMP requirements and with the evolution toward

more stringent criteria because both are consistent with practices in the larger field of quality assurance and with device manufacturing experience. However, whether or not the more stringent criteria actually improve the quality of medical devices depends upon the technical competence of FDA inspectors. FDA did not attempt to assess the actual impact of making these changes at the time when such an assessment could have been done.

Currently, FDA has proposed new GMP requirements, including regulation of the device design process, suppliers of components, and servicing of used devices by manufacturers. These new requirements could improve the GMP program, but whether this happens will not be known unless FDA plans and implements an assessment before and after the new requirements are implemented.

Inspection Organization

FDA has recently taken important steps in the right direction by instituting GMP inspection and certification as a condition for premarket approval of the small group of high-risk devices that must undergo premarket approval, and by initiating a pilot program that monitors the manufacturing practices of another small group of high-risk devices that reach the market through the 510(k) process. The pilot program approach is much less expensive because premarket approval inspections are more comprehensive and because inspections are ordered under the pilot program only when the manufacturer's inspection record, reported in central FDA files, shows the need.

The coordination of inspections with market introduction is important because defects are most likely to occur when devices are first made and used. Market introduction is also the best time to find and to prevent potential design defects from becoming user risks. However, if GMP certification and the pilot program make sense for a small subset of high-risk devices, then they make sense for all high-risk devices because the health and safety consequences of defects are similar for all. FDA is currently exploring whether to expand the pilot program to include all high-risk devices and to require a satisfactory GMP inspection record before these devices are cleared for marketing.

Inspector Qualifications

By making GMP requirements more stringent, CDRH has increased the need for inspector training in specific device technologies. FDA's training of device inspectors is mostly on the job, with classroom courses offered only intermittently. By and large, these training policies develop only limited competency in device technology, and as a result, FDA has trained very few device experts. The agency also does not generally use inspection teams, which would permit these few technical experts to share their expertise.

According to FDA, its training policy permits administrative flexibility in meeting inspection requirements among all FDA-regulated products and facilities. However, FDA's own device experts as well as most of its device inspectors told us that medical devices should be inspected differently than drugs or food because device technology is more diverse and complex and because it changes more rapidly over time. According to this view, better training is needed in order to target inspections to production processes, devices, and manufacturers that are most likely to have significant GMP violations and to make it possible to develop complex causal arguments for compliance enforcement before GMP violations and the resulting device defects have caused serious injury or death.

Based upon information from a variety of sources, we believe these benefits of having better device training are substantial. We found that current FDA training policy and the lack of teamwork restrict the technical depth of device inspections.

Inspection Results

We found that FDA does not meet the statutory minimum obligation to inspect manufacturers of medium- and high-risk devices every 2 years. Depending upon which FDA estimates are used for the inventory of domestic manufacturers, between 41 percent and 57 percent were not inspected during the last 2 years. Furthermore, a recent trend toward fewer inspections each year (with less than 25 percent of the domestic inventory inspected last year) means that the domestic GMP program has been losing its capacity to prevent health and safety risks. For the same set of devices, the frequency of inspections is much lower for foreign manufacturers, on the average about once every 8 years.

According to FDA, the failure to meet the statutory obligation, the recent decline in the number of inspections, and the relatively low frequency of foreign inspections can all be explained by limited resources. In this view, the highest priority inspections come first, and they may involve blood banks or generic drugs instead of devices. Within the devices area, FDA

does target first those device manufacturers who they believe are most likely to have GMP problems.

One consequence of current inspection policy is that many seriously defective devices (i.e., those that could cause serious injury or death) have been marketed and recalled by the manufacturer before undergoing an inspection that could have either prevented the problem or warned FDA to initiate the recall before it was triggered by user experience. Thirty-three percent of domestic manufacturers who had seriously defective devices recalled in fiscal years 1987 through 1990 had not had an inspection in the 2 years before the recall. This problem is likely to be greater for foreign manufacturers because they are inspected less often, and FDA's lack of reporting of these data in central files made it difficult to include them in our analysis.

When inspections did occur within 2 years before recalls of seriously defective devices, and looking only at recalls that were caused by manufacturing problems, 73 percent of these inspections did not find violations that warranted compliance enforcement action. Thus, almost three out of four of these inspections did not help FDA to initiate these recalls before they were triggered by user experience. Limited data and the complexity of inspection and manufacturing processes preclude complete explanation of this result. However, we believe that the relatively large number of failures to find GMP problems may arguably have resulted because poorly trained inspectors failed to find the most important GMP problems.

FDA'S Response to GMP Violations

During fiscal years 1987-90, more than half of all GMP inspections found GMP violations and deficiencies. However, according to FDA district compliance officers, most of these inspections were not violative inspections. In fact, over 84 percent of all inspections found that manufacturers were sufficiently in compliance that no compliance enforcement action was warranted.

According to FDA policy through May 1991, inspection reports that contain the most serious GMP violations should be forwarded to CDRH by district offices, including recommendations for compliance enforcement. However, during fiscal years 1987-90, over 40 percent of these cases were not forwarded to CDRH. Furthermore, it is also FDA policy for districts to report results from the same inspections, with compliance enforcement recommendations, to a central FDA file that includes food and drug inspections as well as devices. However, missing cases and missing data make the

latter file useless for tracking GMP compliance enforcement for medical devices.

Furthermore, these unreported cases and missing data are a cause for concern because they mean that central FDA authorities cannot effectively oversee the nature of the most serious GMP problems and related compliance enforcement actions. Thus, national patterns in manufacturers' failure to comply with the GMP regulation and related FDA enforcement actions may exist but not be recognized as such by the agency.

When cases were forwarded to CDRH, we found most district recommendations for compliance enforcement action were approved. Similarly, when CDRH forwarded recommendations for legal action to the FDA general counsel, most were approved.

We could not assess whether FDA compliance enforcement actions were appropriate. In addition to many inspection results that should have been reported but were not, an assessment is precluded by the fact that district offices are not required to report compliance actions taken in response to the largest category of violative inspections. Ironically, for an agency whose main mission is to oversee quality assurance, FDA has not had an independent review of its own compliance enforcement decisions. However, two recent case studies concluded that FDA was unwilling to enforce immediate correction of serious device defects after districts had uncovered them.[1] We also found that most device inspectors believe that persistent noncompliance with the GMP regulation could be reduced if enforcement actions were more certain and more severe.

Manufacturers' Response to GMP Violations

We tracked device industry behavior over fiscal years 1987-90 in terms of the frequency of inspections that found GMP violations and deficiencies, the number of different types of GMP problems found on these inspections, and the timeliness of corrections once GMP violations had been identified by an inspection or a recall. All of these data indicate that the device industry has not reduced the number of its GMP problems as manufacturers have gained experience with the GMP program, and that GMP violations tend to persist over time.

[1]See Medical Device Safety, Hearings Before the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, 101st Cong., Nov. 6, 1989, and July 17, 1990, and our report entitled Underreporting of Serious Problems With a Home Apnea Monitor, GAO/PEMD-90-17, May 31, 1990.

Limitations of FDA Data Systems

CDRH has developed a number of data systems to help implement device regulations and to evaluate device programs. For program evaluation in particular, the Office of Compliance and Surveillance has documented and analyzed device recalls and monitored device users' experience as the empirical basis for improving GMP regulations and inspections. However, we found that FDA data systems have serious limitations.

First, even though device manufacturers are required to register their manufacturing facilities with FDA, the agency does not know the exact inventory of domestic manufacturers of medium- and high-risk medical devices, and its identification of foreign manufacturers is still less certain. Furthermore, neither inventory has been maintained as a historical record. Consequently, some manufacturers may not have been inspected because they have not been identified by FDA, and the agency cannot track how its inspection responsibilities have evolved over time.

Second, the value of device recall data and user reports of device problems in monitoring the effectiveness of GMP inspections is limited because FDA does not also estimate the inventory of medical devices. Without knowing the number and mix of devices on the market, FDA cannot assess the relative significance of device defects and their associated health and safety risks. Furthermore, without tracking the expanding device inventory over time, and comparing this expansion to the changing number and pattern of recalls, there is no basis to make an overall assessment of whether the GMP program is becoming more or less effective in preventing device defects. This is a particularly important time to begin such tracking if it can be started before FDA implements its proposed new GMP requirements.

In addition to these problems, district offices do not report inspection results and related information that are necessary to monitor GMP program operations. One example was discussed above—not reporting inspection results that justify official compliance enforcement action. We also identified data that districts are not required to report but would nonetheless help to evaluate the effectiveness of inspections.

These failures to report important data, and problems with obsolete and incompatible software and hardware, may be addressed by the new Field Information System that FDA is currently developing and deploying. According to the agency, this system has great potential to reduce the cost of sending and receiving information between district offices and FDA headquarters.

Recommendations

GAO recommends that the Commissioner of FDA:

1. Evaluate the adequacy of its inspection force in light of the increasing competence and experience in device technology needed to conduct device inspections and develop a comprehensive plan to provide adequate technical resources;

2. Meet the statutory obligation for inspecting manufacturers of medium- and high-risk devices;

3. Expand the current pilot program for premarket GMP review of sterile cardiovascular devices to include all high-risk devices;

4. Complete the development and deployment of the new Field Information System in order to achieve comprehensive district reporting of inspection results and compliance actions;

5. Upgrade documentation of the inventory of device manufacturers subject to GMP inspections and develop an inventory of medical devices to serve as benchmarks to assess GMP program effectiveness and the rate of device defects over time; and

6. Assess the impact of proposed new GMP regulations, by monitoring the inspection process and the rate of device defects before and after implementation.

Agency Comments and Our Response

The Department of Health and Human Services (HHS) reviewed a draft of this report, and their response is reprinted in appendix VII. HHS agreed that better training and more specialized assignments would enhance the ability of FDA inspectors to conduct GMP inspections. However, the agency also said that it needs to maximize the utilization of FDA's limited resources by ensuring that its cadre of inspectors can adequately cover emergencies in all areas of FDA responsibility. Furthermore, HHS pointed out that on-the-job training for device inspectors is restricted by the limited size of FDA's inspection force and by the distribution of medical device manufacturers and other regulated manufacturers among FDA districts.

In its concurrence with our recommendation to evaluate the adequacy of the inspection force, HHS said that this evaluation and a training needs assessment are done annually, and that these and other efforts have resulted in an inspection force that is quite capable of doing the type of

inspections required. The agency also stated that the future competency of FDA's field force depends on acquiring additional staff. FDA's fiscal year 1992 budget provides for 55 new field positions in the medical device area, and the agency stated that it needed 214 additional field staff to meet statutory obligations and to perform other field activities concerning medical devices.

We believe that the agency's views—that their current policy yields optimal use of their limited resources, and that they need 214 additional field staff—are not well supported by their written comments. Furthermore, FDA's routine annual assessments of resource requirements do not address all necessary skill requirements for device GMP inspectors, nor do they substitute for a comprehensive needs assessment. We believe such an assessment is required, including the development of benchmark skill requirements, because failure to provide device inspectors with sufficient technical expertise is a major problem in the administration of the device GMP compliance program.

A broad assessment of skill requirements should start from the commonly held view that medical device technology is more diverse and complex than technology embodied in other products inspected by FDA and that device technology changes more rapidly over time. This assessment should also take into account that in recent years FDA has greatly increased the number and complexity of technical observations and judgments expected of device GMP inspectors.

HHS concurred with our recommendation to meet the statutory obligation for inspecting manufacturers of medium- and high-risk devices. However, the agency pointed out that the average time between qualifying inspections is within a few months of the biennial requirement and that the rate of GMP compliance was not significantly affected by such a short delay. Furthermore, HHS asserted that meeting this inspection obligation would require a significant increase in available resources. Finally, the agency emphasized that FDA targets manufacturers and inspection resources where serious problems are most likely to occur.

We agree that FDA may need more inspectors to meet its statutory obligation, particularly once the agency definitely identifies all manufacturers of medium- and high-risk devices (see discussion of device registration and listing below). However, the need for additional inspectors and the effectiveness of inspection targeting are difficult to document because of

many gaps in FDA's reporting of GMP inspection activities and compliance outcomes.

Regarding our recommendation on the coordination of GMP inspections with the market introduction of new medical devices, HHS stated that it is exploring the feasibility of expanding the pilot program for premarket GMP inspections to manufacturers of all new critical medical devices. The agency warned that such an expansion may depend upon getting additional resources because of the large number of devices undergoing premarket review. The agency also raised concern that adding a new inspection requirement could delay market introduction.

HHS concurred with our recommendation to complete development and deployment of the new Field Information System in order to achieve comprehensive district reporting of inspection results and compliance actions. We commend the agency for planning and proceeding to reengineer communications between field offices and all other components of the agency, including the development of a common data base and elimination of costly duplicative data entry.

We are, however, concerned that FDA data systems are currently designed mainly or only for the purpose of short-term program management. The new Field Information System should also help to make device regulatory activities and results transparent to public oversight. In addition to the data reporting needs identified in this report, outside reviewers suggested that FDA should report GMP violations and deficiencies by their Code of Federal Regulation number. (Appendix VI contains a list of our outside reviewers.) While these added information demands would increase the planning time and resources needed for the new information system, they could also decrease the future need for oversight investigations.

HHS concurred with the first part of our recommendation to upgrade the agency's inventory of device manufacturers and to develop an inventory of medical devices. To upgrade its inventory of device manufacturers, the agency has recently upgraded its device product coding system to assist manufacturers in listing their devices, and it is moving to integrate the process by which manufacturers list their devices and register their manufacturing sites. Both changes should improve FDA's capacity to identify manufacturing sites where medium- and high-risk devices should be inspected every 2 years. We were unable to review these changes because they were still in development during the data-gathering phase of our evaluation.

Regarding the development of an inventory of medical devices, the agency indicated that FDA has long recognized the potential value of an inventory of medical devices in distribution and use. However, the agency pointed out that the Food, Drug, and Cosmetic Act does not require manufacturers or user facilities to document such information, nor is there any comprehensive source of such data in the private sector. The agency also indicated that sampling manufacturers and user facilities would be costly, and it would be difficult to extrapolate to the entire industry. Nevertheless, the agency indicated that it is exploring the feasibility of requiring device manufacturers to report relevant data as part of expanded user reporting regulations required by the Safe Medical Devices Act of 1990.

HHS concurred with our recommendation to assess the impact of proposed new GMP regulations by monitoring the inspection process and outcomes before and after implementation. We commend FDA for having data bases in place, particularly the Recall Problem Cause data set, which should facilitate measurement of device experience before and after the new regulations are implemented.

Request Letter

U.S. House of Representatives
Subcommittee on Oversight and Investigations
of the
Committee on Energy and Commerce
Washington, DC 20515

January 19, 1990

The Honorable Charles A. Bowsher
Comptroller General of the United States
U.S. General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Bowsher:

The Medical Device Amendments of 1976 (the Act) authorizes the Food and Drug Administration (FDA) as part of general controls, to require manufacturers to develop and adhere to good manufacturing practices. The good manufacturing practices (GMPs) regulations serve as a framework for the development of individualized quality assurance programs. Such practices include controls over manufacturing specifications and processing procedures, device components, packaging and labeling, and manufacturing equipment and records.

During the Subcommittee's investigation into the manufacturing and marketing of medical devices, it has become clear that in the absence of other intended controls such as performance standards, and with the large-scale avoidance of premarket approval requirements through the use of section 510(k) of the Act, GMPs have become the primary means -- apart from problem reporting -- available to the FDA to ensure the safety and efficacy of almost 90 percent of the medical devices currently marketed in the U.S.

The recent work of your Program Evaluation and Methodology Division, however, raises concerns about the effectiveness of even this control. The reports entitled Medical Device Recalls: An Overview and Analysis 1983-88, (GAO/PEMD-89-15BR) and Medical Device Recalls: Examination of Selected Cases, (GAO/PEMD-90-6) shows that a large proportion of medical device recalls results from design and manufacturing problems, suggesting that there may be a need for major improvements in industry GMPs as well as the FDA's surveillance of industry practice.

With this in mind, the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce is requesting that GAO undertake a study that would: (1) describe and analyze the structures and procedures the FDA has established to promote good manufacturing practices, including the requirements established by regulation and official agency guidelines; (2) identify any critical elements of generally accepted quality assurance programs not specifically addressed by either FDA regulations or guidelines; (3) determine what data the FDA has obtained about manufacturers' implementation of existing GMP requirements, including identification of patterns and trends in the findings of GMP inspections and identification of any specific areas of GMPs in which there are widespread violations; (4) assess the quality and limitations of the information available to the FDA on the status of device manufacturing practices, including quality assurance programs; and (5) determine what actions the FDA has taken to assure manufacturers' adherence to the GMP requirements.

We are requesting that this study give particular attention to industry practices and FDA surveillance activities relating to the GMP requirements on process validation and to the status of industry and FDA efforts in achieving "Preproduction Quality Assurance Planning" (See FDA Guideline, September 1989). We are particularly interested in the status of GMPs for manufacturers of critical devices.

Thank you for your cooperation. If you have any questions about this request, please contact Claudia Beville of the Subcommittee staff at 225-4441.

Sincerely,

John D. Dingell
Chairman
Subcommittee on
Oversight and Investigations

The GMP Regulation

PART 820—GOOD MANUFACTURING PRACTICE FOR MEDICAL DEVICES: GENERAL

AUTHORITY: Secs. 501, 502, 518, 519, 520(f), 701(a), 52 Stat. 1049-1051 as amended, 1055, 90 Stat. 562-569 (21 U.S.C. 351, 352, 360h, 360i, 360j(f), 371(a)).

SOURCE: 43 FR 31508, July 21, 1978, unless otherwise noted.

Subpart A—General Provisions

§ 820.1 Scope.

The regulation set forth in this part describes current good manufacturing practices for methods used in, and the facilities and controls used for, the manufacture, packing, storage, and installation of all finished devices intended for human use. The regulation is intended to assure that such devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act. Part 820 establishes basic requirements applicable to finished devices, including additional requirements for critical devices. This regulation is not intended to apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidelines. Manufacturers of human blood and blood components are not subject to this part, but are subject to Part 606 of this chapter.

(a) *Authority.* This Part 820 is established and promulgated under authority of sections 501, 502, 518, 519, 520(f), and 701(a) of the act (21 U.S.C. 351, 352, 360h, 360i, 360j(f), and 371(a)). The failure to comply with any applicable provisions in Part 820 in the manufacture, packing, storage, or installation of a device renders the device adulterated under section

501(h) of the act. Such a device, as well as the person responsible for the failure to comply, is subject to regulatory action.

(b) *Limitations.* The current good manufacturing practice regulation in Part 820 supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event it is impossible to comply with applicable regulations both in this part and in other parts of this chapter, the regulations specifically applicable to the device in question shall supersede any other regulations.

(c) *Applicability.* The provisions of Part 820 shall be applicable to any finished device, as defined in this part, intended for human use, that is manufactured, imported, or offered for import in any State or territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(d) *Exemptions or variances.* Any person who wishes to petition for an exemption or variance from any device good manufacturing practice requirement is subject to the requirements of section 520(f)(2) of the act. Petitions for an exemption or variance shall be submitted according to the procedures set forth in § 10.30 of this chapter, the Food and Drug Administration's administrative procedures. Guidance is available from the Bureau of Medical Devices, Division of Compliance Programs, Industry Programs Branch (HFK-132), 8757 Georgia Ave., Silver Spring, MD 20910; telephone 301-427-7194.

[43 FR 31508, July 21, 1978, as amended at 44 FR 75628, Dec. 21, 1979]

§ 820.3 Definitions.

(a) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321-392)).

(b) "Audit" means a documented activity performed in accordance with written procedures on a periodic basis to verify, by examination and evaluation of objective evidence, compliance with those elements of the quality assurance program under review. "Audit" does not include surveillance or inspection activities performed for the purpose of conducting a quality assurance program or undertaking complaint investigations or failure analyses of a device.

(c) "Component" means any material, substance, piece, part, or assembly used during device manufacture which is intended to be included in the finished device.

(d) "Control number" means any distinctive combination of letters or numbers, or both, from which the complete history of the manufacture, control, packaging, and distribution of a production run, lot, or batch of finished devices can be determined.

(e) "Critical component" means any component of a critical device whose failure to perform can be reasonably expected to cause the failure of a critical device or to affect its safety or effectiveness.

(f) "Critical device" means a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user. Critical devices will be identified by the Commissioner after consultation with the Device Good Manufacturing Practice Advisory Committee authorized under section 520(f) of the act, and an illustrative list of critical devices will be available from the Bureau of Medical Devices, Food and Drug Administration.

(g) "Critical operation" means any operation in the manufacture of a critical device which, if improperly performed, can be reasonably expected to cause the failure of a critical device or to affect its safety or effectiveness.

(h) "Device history record" means a compilation of records containing the complete production history of a finished device.

(i) "Device master record" means a compilation of records containing the design, formulation, specifications, complete manufacturing procedures, quality assurance requirements, and labeling of a finished device.

(j) "Finished device" means a device, or any accessory to a device, which is suitable for use, whether or not packaged or labeled for commercial distribution.

(k) "Manufacturer" means any person, including any repacker and/or relabeler, who manufactures, fabricates, assembles, or processes a finished device. The term does not include any person who only distributes a finished device.

(l) "Manufacturing material" means any material such as a cleaning agent, mold-release agent, lubricating oil, or other substance used to facilitate a manufacturing process and which is not intended by the manufacturer to be included in the finished device.

(m) "Noncritical device" means any finished device other than a critical device.

(n) "Quality assurance" means all activities necessary to assure and verify confidence in the quality of the process used to manufacture a finished device.

§ 820.5 Quality assurance program.

Every finshed device manufacturer shall prepare and implement a quality assurance program that is appropriate to the specific device manufactured and meets the requirements of this part.

Subpart B—Organization and Personnel

§ 820.20 Organization.

Each manufacturer shall have in place an adequate organizational structure and sufficient personnel to assure that the devices the manufacturer produces are manufactured in accordance with the requirements of this regulation. Each manufacturer shall prepare and implement quality assurance procedures adequate to assure that a formally established and documented quality assurance program is performed. Where possible, a designated individual(s) not having direct responsibility for the performance of a manufacturing operation shall be responsible for the quality assurance program.

(a) *Quality assurance program requirements.* The quality assurance program shall consist of procedures adequate to assure that the following functions are performed:

(1) Review of production records;

(2) Approval or rejection of all components, manufacturing materials, in-process materials, packaging materials, labeling, and finished devices; approval or rejection of devices manufactured, processed, packaged, or held under contract by another company;

(3) Identifying, recommending, or providing solutions for quality assurance problems and verifying the implementation of such solutions; and

(4) Assuring that all quality assurance checks are appropriate and adequate for their purpose and are performed correctly.

(b) *Audit procedures.* Planned and periodic audits of the quality assurance program shall be implemented to verify compliance with the quality assurance program. The audits shall be performed in accordance with written procedures by appropriately trained individuals not having direct responsibilities for the matters being audited. Audit results shall be documented in written audit reports, which shall be reviewed by management having responsibility for the matters audited. Followup corrective action, including reaudit of deficient matters, shall be taken when indicated. An employee of the Food and Drug Administration, designated by the Food and Drug Administration, shall have access to the written procedures established for the audit. Upon request of such an employee, a responsible official of the manufacturer shall certify in writing that the audits of the quality assurance program required under this paragraph have been performed and documented and that any required corrective action has been taken.

§ 820.25 Personnel.

Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all operations are correctly performed.

(a) *Personnel training.* All personnel shall have the necessary training to perform their assigned responsibilities adequately. Where training programs are necessary to assure that personnel have a thorough understanding of their jobs, such programs shall be conducted and documented. All employees

shall be made aware of device defects which may occur from the improper performance of their specific jobs. Quality assurance personnel shall be made aware of defects and errors likely to be encountered as part of their quality assurance functions.

(b) *Personnel health and cleanliness.* Personnel in contact with a device or its environment shall be clean, healthy, and suitably attired where lack of cleanliness, good health, or suitable attire could adversely affect the device. Any personnel who, by medical examination or supervisory observation, appear to have a condition which could adversely affect the device shall be excluded from affected operations until the condition is corrected. Personnel shall be instructed to report such conditions to their supervisors.

Subpart C—Buildings

§ 820.40 Buildings.

Buildings in which manufacturing, assembling, packaging, packing, holding, testing, or labeling operations are conducted shall be of suitable design and contain sufficient space to facilitate adequate cleaning, maintenance, and other necessary operations. The facilities shall provide adequate space designed to prevent mixups and to assure orderly handling of the following: Incoming components; rejected or obsolete components; in-process components; finished devices; labeling; devices that have been reprocessed, reworked, or repaired; equipment; molds, patterns, tools, records, drawings, blueprints; testing and laboratory operations; and quarantined products.

§ 820.46 Environmental control.

Where environmental conditions at the manufacturing site could have an adverse effect on a device's fitness for use, these environmental conditions shall be controlled to prevent contamination of the device and to provide proper conditions for each of the operations performed pursuant to § 820.40. Conditions to be considered for control are lighting, ventilation, temperature, humidity, air pressure, filtration, airborne contamination, and other contamination. Any environmental control system shall be periodically inspected to verify that the system is properly functioning. Such inspections shall be documented.

§ 820.56 Cleaning and sanitation.

There shall be adequate written cleaning procedures and schedules to meet manufacturing process specifications. Such procedures shall be provided to appropriate personnel.

(a) *Personnel sanitation.* Washing and toilet facilities shall be clean and adequate. Where special clothing requirements are necessary to assure that a device is fit for its intended use, clean dressing rooms shall be provided for personnel.

(b) *Contamination control.* There shall be procedures designed to prevent contamination of equipment, components, or finished devices by rodenticides, insecticides, fungicides, fumigants, hazardous substances, and other cleaning and sanitizing substances. Such procedures shall be documented.

(c) *Personnel practices.* Where eating, drinking, and smoking by personnel could have an adverse effect on a device's fitness for use, such practices shall be limited to designated areas selected so as to avoid such an adverse effect.

(d) *Sewage and refuse disposal.* Sewage, trash, by-products, chemical effluents, and other refuse shall be disposed of in a timely, safe, and sanitary manner.

Subpart D—Equipment

§ 820.60 Equipment.

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

(a) *Maintenance schedule.* Where maintenance of equipment is necessary to assure that manufacturing specifications are met, a written schedule for the maintenance, adjustment, and cleaning of equipment shall be developed and adhered to. Such schedule shall be visibly posted on or near each piece of equipment, or be readily available to personnel performing mainte-

nance activities. A written record shall be maintained documenting when scheduled maintenance activities are performed.

(b) *Inspection.* Periodic documented inspections shall be made to assure adherence to applicable equipment maintenance schedules.

(c) *Adjustment.* Any inherent limitations or allowable tolerances shall be visibly posted on or near equipment requiring periodic adjustments, or be readily available to personnel performing these adjustments.

(d) *Manufacturing material.* Manufacturing material, including a cleaning agent, mold-release agent, lubricating oil, or other substance used on or in the manufacturing equipment or the device, shall be subsequently removed from the device or limited to a specified amount that does not adversely affect the device's fitness for use. There shall be written procedures for the use and removal of such manufacturing material. The removal of such manufacturing material shall be documented.

§ 820.61 Measurement equipment.

All production and quality assurance measurement equipment, such as mechanical, automated, or electronic equipment, shall be suitable for its intended purposes and shall be capable of producing valid results. Such equipment shall be routinely calibrated, inspected, and checked according to written procedures. Records documenting these activities shall be maintained. When computers are used as part of an automated production or quality assurance system, the computer software programs shall be validated by adequate and documented testing. All program changes shall be made by a designated individual(s) through a formal approval procedure.

(a) *Calibration.* Calibration procedures shall include specific directions and limits for accuracy and precision. There shall be provisions for remedial action when accuracy and precision limits are not met. Calibration shall be performed by personnel having the necessary education, training, background, and experience.

(b) *Calibration standards.* Where practical, the calibration standards used for production and quality assurance measurement equipment shall be traceable to the national standards of the National Bureau of Standards, Department of Commerce. If national standards are not practical for the parameter being measured, an independent reproducible standard shall be used. If no applicable standard exists, an in-house standard shall be developed and used.

(c) *Calibration records.* The calibration date, the calibrator, and the next calibration date shall be recorded and displayed, or records containing such information shall be readily available for each piece of equipment requiring calibration. A designated individual(s) shall maintain a record of calibration dates and of the individual performing each calibration.

Subpart E—Control of Components

§ 820.80 Components.

Components used in manufacturing shall be received, stored, and handled in a manner designed to prevent damage, mixup, contamination, and other adverse effects. Components shall be quarantined prior to acceptance or clearly identified as not yet accepted.

(a) *Acceptance of components.* There shall be a written procedure for acceptance of components. A designated individual(s) shall accept or reject components. A record shall be maintained of component acceptance and rejection. Upon receipt, each shipping container of components shall be visually examined for damage. Where deviations from component specifications could result in the device being unfit for its intended use, components shall be inspected, sampled, and tested for conformance to specifications.

(b) *Storage and handling of components.* If the quality or fitness for use of components deteriorates over time, the components shall be stored in a manner to facilitate proper stock rotation. Component control numbers or other identifications shall be easily viewable. All obsolete, rejected, or deteriorated components shall be clearly identified and segregated from accepted components. Records shall be main-

tained of the disposition of all obsolete, rejected, or deteriorated components.

§ 820.81 Critical devices, components.

In addition to the requirements of § 820.80, the following requirements apply to critical devices:

(a) *Acceptance of critical components.* There shall be written procedures for the accepting, sampling, testing, and inspecting of all lots of critical components to assure that critical components conform to specifications. The number of units sampled from each lot of critical components shall be based upon an acceptable statistical rationale, the past quality history of the supplier, and the quantity needed for analysis and reserve. Each lot of critical components shall be identified with a control number(s) upon receipt. The percentage of defective critical components for each lot and the percentage of lots rejected shall be recorded and identified by supplier name.

(b) *Critical component supplier agreement.* Where possible, the manufacturer shall secure from the critical component supplier a written agreement whereby the supplier agrees to notify the manufacturer of any proposed change in a critical component. Where such an agreement exists, the manufacturer shall not accept such a change until the manufacturer has determined the impact of the change on the finished device.

Subpart F—Production and Process Controls

§ 820.100 Manufacturing specifications and processes.

Written manufacturing specifications and processing procedures shall be established, implemented, and controlled to assure that the device conforms to its original design or any approved changes in that design.

(a) *Specification controls.* (1) Procedures for specification control measures shall be established to assure that the design basis for the device, components, and packaging is correctly translated into approved specifications.

(2) Specification changes shall be subject to controls as stringent as those applied to the original design specifications of the device. Such changes shall be approved and documented by a designated individual(s) and shall include the approval date and the date the change becomes effective.

(b) *Processing controls.* (1) Where deviations from device specifications could occur as a result of the manufacturing process itself, there shall be written procedures describing any processing controls necessary to assure conformance to specifications.

(2) All processing control operations shall be conducted in a manner designed to assure that the device conforms to applicable specifications.

(3) There shall be a formal approval procedure for any change in the manufacturing process of a device. Any approved change shall be communicated to appropriate personnel in a timely manner.

§ 820.101 Critical devices, manufacturing specifications, and processes.

In addition to the requirements of § 820.100, the following requirements apply to critical devices:

(a) *Critical operation performance.* Any critical operation shall be performed by a suitable designated individual(s) or suitable equipment and shall be verified.

(b) *Record of critical operation.* Any individual responsible for the performance of a critical operation shall record or reference that operation in the device history record as required in § 820.185.

§ 820.115 Reprocessing of devices or components.

(a) Reprocessing procedures shall be established, implemented, and controlled to assure that the reprocessed device or component meets the original, or subsequently modified and approved, specifications.

(b) Any device rejected during finished device inspection and later reprocessed shall be subject to another complete final inspection for any characteristic of the device which may be

adversely affected by such reprocessing.

§ 820.116 Critical devices, reprocessing of devices or components.

In addition to the requirements of § 820.115, the following requirements apply to critical devices:

(a) *Reprocessing procedures.* There shall be written procedures for any reprocessing associated with the production of a critical device or component. These procedures shall prescribe the equipment to be used in reprocessing and shall include any special quality assurance methods or tests. The procedures shall be designed so that the reprocessed device or component meets the original, or subsequently modified and approved, specifications. The procedures shall be designed to prevent adulteration, e.g., because of material, structural, or molecular change in the device or component due to reprocessing. Special care shall be taken to assure that the device or component to be reprocessed is clearly identified and separated from like devices or components not to be reprocessed. When there is constant reprocessing of a device or component, a determination of the effect of the reprocessing upon the device or component shall be made and documented. There shall be a formal approval procedure for instituting a new, or altering an approved, reprocessing procedure.

(b) *Reprocessing control.* Any critical device or component subject to reprocessing procedures shall conform to the original, or subsequently modified and approved, specifications. Written testing and sampling procedures to assure such comformity shall be contained or referenced in the device master record. Any prior quality assurance check shall be repeated on the reprocessed device or component if the reprocessing could adversely affect any performance characteristic previously inspected.

Subpart G—Packaging and Labeling Control

§ 820.120 Device labeling.

There shall be adequate controls to maintain labeling integrity and to prevent labeling mixups.

(a) *Label integrity.* Labels shall be designed, printed, and applied so as to remain legible during the customary conditions of processing, storage, handling, distribution, and use. Labels and other labeling shall not be released to inventory until a designated individual has proofread samples of the labeling for accuracy.

(b) *Separation of operations.* Each labeling or packaging operation shall be separated physically or spatially in a manner designed to prevent mixups.

(c) *Area inspection.* Prior to the implementation of any labeling or packaging operation, there shall be an inspection of the area where the operation is to occur by a designated individual to assure that devices and labeling materials from prior operations do not remain in the labeling or packaging area. Any such items found shall be destroyed, disposed of, or returned to storage prior to the onset of a new or different labeling or packaging operation.

(d) *Storage.* Labels and labeling shall be stored and maintained in a manner that provides proper identification and is designed to prevent mixups.

(e) *Labeling materials.* Labeling materials issued for devices shall be examined for identity and, where applicable, the correct expiration date, control number, storage instructions, handling instructions, and additional processing instructions. A record of such examination, including the date and person performing the examination, shall be maintained in the device history record.

§ 820.121 Critical devices, device labeling.

In addition to the requirements of § 820.120, the following requirements apply to critical devices:

(a) *Control number.* Labels issued for critical devices shall contain a control number.

(b) *Labeling check.* The signature of the individual who proofreads the

labels and other labeling, and the date of the proofreading, shall be recorded.

(c) *Access restriction.* Access to the labels and other labeling shall be restricted to authorized personnel.

§ 820.130 Device packaging.

The device package and any shipping container for a device shall be designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.

Subpart H—Holding, Distribution, and Installation

§ 820.150 Distribution.

There shall be written procedures for warehouse control and distribution of finished devices to assure that only those devices approved for release are distributed. Where a device's fitness for use or quality deteriorates over time, there shall be a system to assure that the oldest approved devices are distributed first.

§ 820.151 Critical devices, distribution records.

In addition to the requirements of § 820.150, adequate distribution records for critical devices shall include, or make reference to the location of: the name and address of the consignee, the name and quantity of devices, the date shipped, and the control number used. These records shall be retained as required by § 820.180(b).

§ 820.152 Installation.

Where a device is installed by the manufacturer or its authorized representative, the manufacturer or representative shall inspect the device after installation to assure that the device will perform as intended. Where a device is installed by a person other than the manufacturer or its authorized representative, the manufacturer shall provide adequate instructions and procedures for proper installation.

Subpart I—Device Evaluation

§ 820.160 Finished device inspection.

There shall be written procedures for finished device inspection to assure that device specifications are met. Prior to release for distribution, each production run, lot or batch shall be checked and, where necessary, tested for conformance with device specifications. Where practical, a device shall be selected from a production run, lot or batch and tested under simulated use conditions. Sampling plans for checking, testing, and release of a device shall be based on an acceptable statistical rationale. Finished devices shall be held in quarantine or otherwise adequately controlled until released.

§ 820.161 Critical devices, finished device inspection.

In addition to the requirements of § 820.160, the following requirement applies to critical devices: A critical device or component which does not meet its performance specifications shall be investigated. A written record of the investigation, including conclusions and followup, shall be made. A critical device shall not leave the control of the manufacturer for distribution until all acceptance records and test results have been checked by a designated individual(s). Such individual(s) shall assure that all records and documentation required for the device history record are present and complete, and show that release of the device was consistent with the release criteria. Such individual(s) shall authorize, by signature, the release of the device for distribution.

§ 820.162 Failure investigation.

After a device has been released for distribution, any failure of that device or any of its components to meet performance specifications shall be investigated. A written record of the investigation, including conclusions and followup, shall be made.

Subpart J—Records

§ 820.180 General requirements.

All records required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to employees of the Food and Drug Administration designated to perform inspections. Such records shall be available for review and copying by such employees. Except as specifically provided elsewhere, the following general provisions shall apply to all records required by this part.

(a) *Confidentiality.* Those records deemed confidential by the manufacturer may be marked to aid the Food and Drug Administration in determining whether information may be disclosed under the public information regulation in Part 20 of this chapter.

(b) *Record retention period.* All required records pertaining to a device shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer. Photostatic or other reproductions of records required by this part may be used.

§ 820.181 Device master record.

The device master record shall be prepared, dated, and signed by a designated individual(s). Any changes in the device master record shall be authorized in writing by the signature of a designated individual(s). Any approval forms shall be part of the device master record. The device master record for each type of device shall include, or refer to the location of, the following information:

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

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

(c) Quality assurance procedures and specifications including quality assurance checks used and the quality assurance apparatus used.

(d) Packaging and labeling specifications including methods and processes used.

§ 820.182 Critical devices, device master record.

In addition to the requirements of § 820.181, the device master record for a critical device shall include or refer to the location of the following information:

(a) *Critical components and critical component suppliers.* Full information concerning critical components and critical component suppliers, including the complete specifications of all critical components, the sources where they may be obtained, and written copies of any agreements made with suppliers under § 820.81(b).

(b) *Labels and labeling.* Complete labeling procedures for the individual device and copies of all approved labels and other labeling.

§ 820.184 Device history record.

A device history record shall be maintained to demonstrate that the device is manufactured in accordance with the device master record. The device history record shall include, or refer to the location of, the following information: The dates of manufacture, the quantity manufactured, the quantity released for distribution, and any control number used.

§ 820.185 Critical devices, device history record.

In addition to the requirements of § 820.184, the following requirements apply to critical devices: There shall be a critical device history record for each control number, which shall include complete information relating to the production unit. This record shall identify the specific label, labeling, and control number used for each production unit and shall be readily accessible and maintained by a designated individual(s). The device history record shall include, or refer to the location of, the following:

(a) *Component documentation.* The documentation of each critical component used in the manufacture of a device shall include:

(1) *Control number.* The control number designating each critical component or lot of critical components used in the manufacture of a device.

(2) *Acceptance record.* The acceptance record of the critical component, including acceptance date and signature of the recipient.

(b) *Record of critical operation.* The record of, or reference to, each critical operation, identifying the date performed, the designated individual(s) performing the operation and, when appropriate, the major equipment used.

(c) *Inspection checks.* The inspection checks performed, the methods and equipment used, results, the date, and signature of the inspecting individual.

§ 820.195 Critical devices, automated data processing.

When automated data processing is used for manufacturing or quality assurance purposes, adequate checks shall be designed and implemented to prevent inaccurate data output, input, and programming errors.

§ 820.198 Complaint files.

(a) Written and oral complaints relative to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device shall be reviewed, evaluated, and maintained by a formally designated unit. This unit shall determine whether or not an investigation is necessary. When no investigation is made, the unit shall maintain a record that includes the reason and the name of the individual responsible for the decision not to investigate.

(b) Any complaint involving the possible failure of a device to meet any of its performance specifications shall be reviewed, evaluated, and investigated. Any complaint pertaining to injury, death, or any hazard to safety shall be immediately reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint file.

(c) When an investigation is made, a written record of each investigation shall be maintained by the formally designated unit identified in paragraph (a) of this section. The record of investigation shall include the name of the device, any control number used, name of complainant, nature of complaint, and reply to complainant.

(d) Where the formally designated unit is located at a site separate from the actual manufacturing establishment, a duplicate copy of the record of investigation of any complaint shall be transmitted to and maintained at the actual manufacturing establishment in a file designated for device complaints.

The Organization and Evolution of GMP Requirements

GMP subpart or subsection	1978 GMP requirement	Incremental changes in GMP requirements as of 1990
A. General Provisions	Scope of authority and definitions	
B. Organization and Personnel		
Organization (820.20)	Adequate organization and sufficient personnel to ensure compliance with part 820 of the GMP regulation Adequate quality assurance program Adhere to written procedures for periodic audits, audit staff shall be appropriately trained	
Personnel (820.25)	Sufficient personnel to ensure correct performance of all operations Adequate training for all personnel to perform assigned responsibilities Clean, healthy, and suitably attired personnel	
C. Buildings		
Buildings (820.40)	Adequate design and sufficient space to facilitate cleaning, maintenance, and necessary operations	
Environmental control (820.46)	Proper controls to prevent contamination and to provide proper conditions for operations	
Cleaning and sanitation (820.56)	Adequate written cleaning procedures Adequate personnel sanitation facilities	
D. Equipment		
Equipment (820.60)	Adequate to facilitate maintenance, adjustment, cleaning Adhere to maintenance and inspection schedule Adhere to written procedures for the use and removal of contaminating manufacturing material from devices	Adequate equipment for intended use in manufacturing process

(continued)

GMP subpart or subsection	1978 GMP requirement	Incremental changes in GMP requirements as of 1990
Measurement equipment (820.61)	Suitable for intended purposes	
	Adhere to routine calibration procedures	
	Adequate and documented software testing	
	Adequate personnel to perform calibration	
	Record and display calibration information for each piece of equipment	
	Adhere to national calibration standards when practical	
E. Control of Components		
Components (820.80)	Adequate handling and storage procedure to prevent damage, mixup, contamination, and adverse effects	
	Adhere to written procedures for acceptance of components	Adequate acceptance testing will be based on accepted statistical rationale
Critical components (820.81)	Adhere to written sampling, testing, and inspection procedures for acceptance of critical components	
	Seek written agreement with supplier to notify manufacturer of any component changes	
F. Production and Process Controls		
Manufacturing specifications and processes (820.100)	Written specifications and procedures	Adequate process validation
	Adhere to specification control procedures	Adequate qualification and validation of specification changes
	Adhere to specification change procedures	
	Adhere to processing control procedures	
	Adhere to processing change control procedures	
Critical devices, manufacturing specifications, and processes (820.101)	Suitable personnel and equipment for critical operations	
	Documentation by responsible individuals in device history record	
Reprocessing of devices or components (820.115)	Adhere to reprocessing procedures	Adequate control of nonconforming devices or components
Critical devices, reprocessing of devices or components (820.116)	Adhere to written reprocessing procedures for critical devices or components	
	Adhere to formal reprocessing change procedure	

(continued)

GMP subpart or subsection	1978 GMP requirement	Incremental changes in GMP requirements as of 1990
G. Packaging and Labeling Control		
Device Labeling (820.120)	Adequate controls to maintain label integrity and to prevent labeling mixups	
Critical devices, device labeling (820.121)	Include control number on label Record signature of proofreader of label and date Access restricted to authorized personnel	
Device packaging (820.130)	Adequate to protect device from alteration and damage	
H. Holding, Distribution, and Installation		
Distribution (820.150)	Adhere to written procedures for warehouse control and distribution, including system to ensure stock rotation	
Critical devices (820.151)	Records to contain detailed information on distribution including name and address of consignee, quantity and date shipped, and control numbers	
Installation (820.152)	Adequate installation by manufacturer or instructions and procedures for proper installation by third party	
I. Device Evaluation		
Finished device inspection (820.160)	Adhere to written procedures for finished device inspection prior to release for distribution	
Critical devices, finished device inspection (820.161)	Adhere to procedures for investigating critical devices that do not meet specifications All acceptance records and test results have been checked by designated individuals	
Failure investigation (820.162)	Investigate and document any failure after release to distribution	Adequate failure investigation including causes and corrective action taken

(continued)

GMP subpart or subsection	1978 GMP requirement	Incremental changes in GMP requirements as of 1990
J. Records		
General requirements (820.180)	Maintain all required records for at least 2 years in an accessible place where they can be reviewed and copied by FDA	
Device master record (820.181)	Adequate device master records	
Critical devices, device master (820.182)	Adequate critical device master record, including additional details about components, suppliers, and labeling	
Device history record (820.184)	Adequate device history record	
Critical devices, device history (820.185)	Adequate critical device history records by control number including complete information about production unit and production process	
Critical devices, automated data processing (820.195)	Adequate checks on data input, output, and programming	
Complaint files (820.198)	Document, review, and evaluate all complaints by designated unit	Adequate specification of failure investigation procedures
	Investigate all complaints involving possible device failure or any pertaining in any way to death or health hazard	Adequate record of the investigation and corrective action taken
		Adequate complaint analysis procedures

Survey Methodology

Survey Methodology

Information on the number, education, experience, and perspective of device GMP inspectors was gathered by surveying the population with a mailed questionnaire. This appendix presents information on the methods employed in developing and administering the survey.

The Universe

The universe of interest consists of all FDA inspectors who are available for assignment to perform medical device GMP inspections. The population list was constructed from names of inspectors provided by FDA district office administrators. We asked the district offices to provide the names of the inspectors they considered qualified or highly qualified to perform device GMP inspections. The latter are those who would be selected first to do complex device inspections. The former also do device inspections but do not receive the same preference in doing complex inspections. We identified 329 inspectors who were considered either qualified or highly qualified to perform GMP inspections. Seventy-four percent (244) were characterized as qualified, the remaining 26 percent (85) were characterized as highly qualified.

Survey Administration

The survey instrument consisted of a 6-page confidential questionnaire containing 14 questions. The structure of the questions included limited and open-ended response options. The questionnaire was pretested with five FDA inspectors drawn from the universe list. Each questionnaire packet included a self-addressed business reply envelope, an explanatory cover letter, and the questionnaire.

Response Rate

Two hundred sixty-two completed questionnaires were returned before the initiation of our analysis, resulting in a 79-percent response rate. Of the total responses analyzed, 76 percent were from qualified inspectors and 24 percent were from highly qualified inspectors. This corresponds with the ratio of qualified to highly qualified in the universe of FDA medical device GMP inspectors. Our analysis is based on this population of respondents.

GMP Violation Categories

Category	Definition
Audits	Quality assurance system audits, procedures and performance are inadequate or absent.
Calibration procedures	Written calibration procedures are inadequate or absent.
Change control procedures	Change control procedures to be followed when making changes are inadequate or absent.
Component or device specification	Secifications for components or finished devices are incomplete or absent.
Complaint handling procedures	Complaint handling procedures such as failure analysis, record-keeping, complaint file maintenance and follow-up are inadequate.
Device history	Device history record is inadequate or absent.
Employee training	Documentation of employee training is inadequate or absent.
Equipment calibration	Equipment calibration procedures and application are inadequate or absent.
Equipment specification	Equipment specifications, maintenance specifications and schedules are inadequate or absent.
Inspection and testing procedures	Inspection and testing procedures for determining conformance to applicable specifications are inadequate or absent.
No change control	Inadequate or no use of controls in making changes in devices, components, processes, master records, and so forth.
No complaint handling procedures	Complaint handling procedures are absent.
Processing procedures	Processing procedures are inadequate or absent.
Process validation	Process validation and qualification of equipment are inadequate or absent.
Record review	Release of in-process devices or finished devices without adequate record review.

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Comments From the Department of Health and Human Services

DEPARTMENT OF HEALTH & HUMAN SERVICES — Office of Inspector General

Washington, D.C. 20201

OCT 11 1991

Mr. Richard L. Linster
Director of Planning and Reporting
United States General
Accounting Office
Washington, D.C. 20548

Dear Mr. Linster:

Enclosed are the Department's comments on your draft report, "Medical Devices: FDA's Regulation of Good Manufacturing Practices." The comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

The Department appreciates the opportunity to comment on this draft report before its publication.

Sincerely yours,

Richard P. Kusserow
Inspector General

Enclosure

COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE GENERAL ACCOUNTING OFFICE (GAO) DRAFT REPORT "MEDICAL DEVICES: FDA'S REGULATION OF GOOD MANUFACTURING PRACTICES"

General Comments

The Department of Health and Human Services shares GAO's concern about the Food and Drug Administration's (FDA) ability to regulate effectively the production and marketing of medical devices. We believe, however, that while the report has identified some areas where improvements are needed, it would be more useful to the Congress if certain aspects were either modified or more fully elaborated.

The report takes issue with FDA's policy of maintaining a generalist investigator cadre to assure that emergencies in all areas of responsibility can be adequately covered. It also takes issue with training provided to investigators assigned to inspect medical devices establishments. While we agree with the report and the investigators who responded to GAO's questionnaire that better training and more specialized assignments would enhance their ability to conduct thorough Good Manufacturing Practices (GMP) inspections, FDA must deploy its inspection force in such a way as to maximize utilization of its limited resources. The report points out that "highly qualified" medical devices inspectors spend only 41 percent of their time on medical device inspections and "qualified" inspectors spend only 25 percent of their time on these inspections. These figures reflect the distribution of medical devices establishments across the nation as well as the need for FDA's limited inspection force (1,000 inspectors) also to provide inspection coverage for all other commodities regulated by FDA. For instance, nationwide, medical devices work comprises only 18 percent of the workload. We cannot devote more time to medical devices without neglecting other obligations such as foods (approximately 40 percent of workload), human drugs (27 percent), biologics (8 percent), and veterinary medicine (7 percent). In districts with a significant device establishment inventory, some investigators are specifically targeted to performing device inspections. This is true of investigators designated as national, regional, and district experts and as medical devices specialists. However, emergency situations in other product lines (e.g. salmon, Tylenol, blood, etc.) have required immediate use of all available investigators.

FDA must maintain the ability to respond to emergencies with all available resources when needed, and the investigators must be adequately trained for all the agency's responsibilities. To this end, we believe it is appropriate to continue FDA's current practice of training the majority of its new investigators to be generalists first and then to specialize

after gaining experience. FDA actively encourages training in specialized areas and as resources have increased, more inspectors are being trained to focus on medical devices. Contrary to the report, FDA has no restrictions against device-specific training. In fact, FDA has initiated several new courses for medical device investigators and revised others to make them more relevant. Each of the new courses is designed to stress efficiency and quality of investigational work. Among the courses recently made available are a new basic medical devices course focusing on GMPs, an industrial sterilization course applicable to both devices and drugs, an advanced medical devices course focusing on current problems, and a course on radiation-producing medical devices. Over the last 18 months, ten medical devices courses have been held for 241 investigators. Additional intermediate level courses are planned for the next fiscal year (FY) in the areas of electronics, in-vitro diagnostic devices, plastic device manufacturing, advanced electronics, and field engineer seminars. Additionally, FDA investigators routinely maintain currency with the published literature in order to enhance their own capabilities. While we cannot disagree that more highly trained investigators are more effective, we believe the above cited courses demonstrate FDA's commitment to excellence.

Finally, while there have been many new developments and technologies introduced in the medical devices arena in the past few years, the statement that "one year away from the industry can render technical knowledge obsolete" may be overly simplistic. Most medical devices are manufactured today using the same technologies that were in use when the GMPs were first established. As indicated above, FDA is and has always taken steps to keep abreast of new developments. Nevertheless, FDA recognizes that it would be desirable to expend more resources on training investigators. As resources are made available, this is taking place.

GAO Recommendation

GAO recommends that the Commissioner of the FDA:

1. Evaluate the adequacy of its inspection force in light of the increasing competence and experience in device technology needed to conduct device inspections, and to develop a comprehensive plan to provide adequate technical resources.

Department Comment

We agree with the need to evaluate continuously the adequacy of FDA's inspection force and provide training where needed. In addition to a yearly assessment of resource requirements, each

year a training needs assessment is conducted to determine how best to meet the ever-changing demands faced by investigators in the field. We believe this and efforts mentioned below have resulted in an inspection force that is quite capable of doing the type of inspections required. As indicated in the report, device investigators average 15 years experience with FDA and more than half of them have at least 9 years experience conducting device inspections. As discussed, the FDA has also significantly increased the number and range of devices courses offered to investigators during the past year. Further, new inspectors are being trained to become device investigators, some within a few weeks or months of entry on duty.

Of equal importance to the future competency of FDA's field force is acquiring additional people. During FY 1991, several new investigators were hired and began training. FDA's FY 1992 budget provides for an additional 55 field positions in the medical devices area. However, we calculate that an additional 214 full time equivalents (FTEs) in the field would be required for FDA to meet its statutory obligations, follow up on reports of defective devices, and implement new legislation. As stated above we are committed to maintaining excellence in all the areas of our investigatory responsibility, including medical devices.

GAO Recommendation

2. Meet the statutory obligation for inspecting manufacturers of medium- and high-risk devices.

Department Comment

We agree that it is desirable to meet the statutory requirements for inspecting manufacturers of medium-to-high-risk devices, and FDA strives to satisfy this requirement. While approximately half of qualifying inspections occur outside this time interval, the average time between qualifying inspections is within a few months of the biennial requirement. A study done by FDA's Office of Planning and Evaluation (OPE) indicates that the rate of compliance by device manufacturers is not significantly affected when the interval between inspections exceeds the biennial requirement by several months. (See "MEDICAL DEVICE QUALIFYING INSPECTIONS-Can We Meet the Biennial Requirements?," annotated briefing charts by Dennis Hill, OPE, FDA, January, 1989).

As stated above, however, to meet the requirements would require a significant increase in available resources. This view was affirmed by a recent Inspector General's study of the

medical device regulatory programs ("FDA Medical Device Regulation From Premarket Review to Recall," Office of Inspector General, Department of Health and Human Services, OEI-09-90-00040, February 1991). The number of FTEs allocated to the device program was increased in FY 1991, and FDA has requested budget authority for an increase in field staffing allocated to device inspections in FY 1992. As the new employees are trained, we can expect that more inspections will be done.

FDA makes every effort to maximize the effectiveness of current resources by targeting manufacturers where serious problems are most likely to occur. As noted in the report, FDA has two levels of GMP inspections. This system is designed to focus the more in-depth inspections where a firm's inspection history, inspection frequency, and reported problems suggest that persistent problems may exist. Furthermore, whenever necessary, FDA employs team inspections to provide the expertise and concentration of forces needed to assure that inspections are comprehensive and effective in identifying deficiencies. While this approach is not perfect, it has been effective in making the best use of available resources. As more resources are made available, FDA will be better able to meet its obligations.

GAO Recommendation

3. Expand the current pilot program for premarket GMP review to include all high-risk devices.

Department Comment

FDA is exploring the feasibility of expanding the pilot program for premarket GMP inspections of manufacturers of new critical medical devices. However, the extent to which the pilot program can be expanded within existing resources is questionable. FDA receives more than 5,000 510(k) submissions per year, the majority of which are for class II and class III devices. FDA must ensure that efforts to increase oversight do not unduly delay market entry. At the same time, the agency must balance premarket oversight with overseeing devices already on the market. FDA is attempting to develop an approach for expanding the pilot program to conform with available resources. Complete implementation may be dependent upon resources becoming available to support the additional workload.

GAO Recommendation

4. Ensure that technical summaries for all devices submitted for premarket review are transmitted to district offices

in order to help them identify changes in technology that should be inspected.

Department Comment

We do not concur. While we support improving communications between the Center for Devices and Radiological Health and FDA's field operations, we do not believe that making manufacturers' 510(k) summaries available to district offices would serve the intended purpose. Under the Safe Medical Devices Act, manufacturers need not submit 510(k) summaries to FDA if they submit statements to the effect that they will make safety and effectiveness information available to any requester. FDA receives summaries for only approximately one-third of the 510(k) submissions. Because they are intended for public disclosure and do not contain trade secrets or confidential information, the summaries generally do not contain detailed technical information or information regarding manufacturing procedures, making their usefulness to investigators of limited value. Furthermore, FDA bases its 510(k) decisions on the information contained in the 510(k) submission, not on the summary. Resource constraints limit the degree to which FDA can review the adequacy of the summaries.

GAO Recommendation

5. Complete the development and deployment of the new Field Information System in order to achieve comprehensive district reporting of inspection results and compliance actions.

Department Comment

We concur. We recognize the deficiencies of FDA's data systems and are working to correct them. A new Field Information System (FIS) has been under development for over a year. The core system is scheduled for installation late in FY 1992, with additional modules to be added. The objective of re-engineering the system is to develop effective interface communication between FDA's Office of Regional Operations and all other components of the agency. This will ultimately provide the means for utilization of a common data base, eliminating the need for duplicative data bases and entry.

GAO Recommendation

6. Upgrade documentation of the inventory of device manufacturers subject to GMP inspections and develop an inventory of medical devices to serve as benchmarks to assess GMP program effectiveness over time.

6

Department Comment

We concur with the need and feasibility of improved device manufacturer registration and device listing. In fact, during the last 3 years, steps have been taken to effect improvements. Among these measures are a new mailout form for annual registration which has resulted in a more thorough and manageable registration process. The computer system utilized for the registration system has also been redesigned and became fully operational in July 1990. Further, the agency has updated device product codes to assist manufacturers in listing their devices. A booklet containing these updated codes is currently being printed and will be made available to all currently registered manufacturers and new registrants in FY 1992. We believe this coding update will contribute to more accurate listing by manufacturers and better identification by FDA of class II and III device manufacturers subject to biennial inspections.

In addition, the device listing system is being revised to integrate it with registration and to strengthen data quality control. A new process is being designed to allow simultaneous registration and listing. This will eliminate the lag between the two processes and will also require that listing be done for each manufacturing site rather than by owner. This change will greatly assist in identifying specific manufacturing sites that require in-depth inspections.

Finally, the new FIS will allow electronic transmission of registration data between FDA headquarters and the field, eliminating the need for redundant data entry.

As for developing an inventory of devices (e.g., "denominator data" giving counts of the number of specific devices in distribution and use), FDA has long recognized the potential value of such information. However, the Federal Food, Drug, and Cosmetic Act does not require device manufacturers or user facilities to supply this information to FDA, and no comprehensive source of this information exists in the private sector. While such information could be obtained on a sampling basis through contracts with hospitals or other sources, this would be costly. Furthermore, it is questionable whether such sampling information would be representative of the entire industry. Nevertheless, FDA is exploring the feasibility of requiring device manufacturers to report selected information of this type as part of revisions to the medical device reporting (MDR) regulations that will accompany user reporting regulations required by the Safe Medical Devices Act of 1990. If it proves not to be feasible to obtain the information this way, we believe the cost of obtaining the information in any meaningful quantity would be prohibitive at this time.

GAO Recommendation

7. Assess the impact of proposed new GMP regulations by monitoring inspection process and outcomes before and after implementation.

Department Comment

We concur. The new GMP regulations are scheduled to be in effect early in 1993. Information currently in FDA's database provides a baseline against which future results can be measured. Approximately 2 years after the new requirements become effective, FDA will have sufficient information to compare the results of the new requirements with current practices. The agency will undertake an assessment of their impact at that time if resources permit.

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Related GAO Products

"Medical Device Problem Reporting: A Case Study of a Home Apnea Monitor," Statement of Carl E. Wisleer (GAO/T-PEMD-90-10; July 17, 1990).

Medical Devices: Underreporting of Serious Problems With a Home Apnea Monitor (GAO/PEMD-90-17; May 31, 1990).

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