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Report to the Chairman, Subcommittee on Health and the Environment, Committee on Energy and Commerce, House of Representatives

August 1988

MEDICAL DEVICES

FDA's 510(k) Operations Could Be Improved

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GAO
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Program Evaluation and
Methodology Division

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August 17, 1988

The Honorable Henry Waxman
Chairman, Subcommittee on Health
and the Environment
Committee on Energy and Commerce
House of Representatives

Dear Mr. Chairman:

This report summarizes GAO's findings on FDA's implementation of the premarket notification provision of the Medical Device Amendments of 1976. As you requested, and as we subsequently agreed with your office, we reviewed FDA's premarket notification policies and day-to-day operations, with particular attention to the determination of substantial equivalence. We also reviewed the implementation of related provisions of the amendments and their implications for premarket notification.

In the report, we make recommendations to the Department of Health and Human Services regarding the need for better documentation of decisions in the premarket notification program and for more consistent policies among the divisions of the Office of Device Evaluation. In addition, the report includes a matter for congressional consideration concerning the need to clarify the meaning of substantial equivalence and to consider alternatives to the current regulatory mechanisms for class II and class III devices. GAO also recommends that the Congress change the statute to permit FDA to use currently marketed devices rather than pre-1976 devices as the comparison in making determinations of substantial equivalence.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 30 days from the date of the report. At that time, we will send copies to the Department of Health and Human Services. We will also make copies available to others upon request. Please call me (202-275-1854) or Lois-ellin Datta (202-275-1370) if you need further information.

Sincerely yours,

Eleanor Chelimsky
Director

Executive Summary

Purpose

Since passage of the Medical Device Amendments of 1976, roughly 36,000 medical devices and device modifications have been marketed subsequent to review by the Food and Drug Administration (FDA). Of those, 94 percent were marketed after FDA, in a review process known as premarket notification (or 510(k) review), found them to be "substantially equivalent" to devices on the market prior to 1976. The remaining 6 percent entered the market after undergoing premarket approval, which is limited to devices that require a more rigorous, empirical demonstration of safety and effectiveness. Concerned about the extensive use of premarket notification as compared to premarket approval, the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce asked the General Accounting Office (GAO) to review FDA's implementation of premarket notification in terms of both formal policies and day-to-day operations. GAO was also asked to identify any problems pertaining to premarket notification resulting from implementation of other provisions of the amendments.

Background

The amendments greatly expanded FDA's authority to regulate medical devices and attempted to both encourage advances in medical technology and protect the public against unsafe and ineffective medical devices. A complex three-tiered system of classification and regulatory control was prescribed. Class I devices (such as bedpans and tongue depressors) are those for which general controls provide reasonable assurance of safety and effectiveness. Class II devices (for example, syringes and hearing aids) require performance standards in addition to general controls. Class III devices (for instance, heart valves and pacemakers) must undergo premarket approval and also comply with general controls.

The premarket notification provision allows FDA to review submissions for devices about to be marketed in order to determine whether they are substantially equivalent to pre-1976 devices. If they are substantially equivalent, they may be marketed. If they are not, the statute automatically places them in class III. The devices are then subject to premarket approval or to reclassification into a lower class before they may be distributed commercially. The statute does not define or otherwise elaborate on the meaning of the term substantial equivalence. The relevant legislative history can be read in different ways. Under one reading, whenever a device about to be marketed varies from a pre-1976 device in its materials, design or energy sources, the product would be found not substantially equivalent and would be subject to premarket approval. Under a less restrictive reading, only variations that could, or

do, materially affect safety or effectiveness should result in a "not substantially equivalent" decision. In any case, a determination of substantial equivalence in the premarket notification process does not mean that a device is safe and effective; it merely indicates that the device under review is not less safe and effective than a comparable pre-1976 device.

Results in Brief

FDA's implementation of the statute is in line with the less restrictive reading of the legislative history, and that reading is duly reflected in FDA's premarket notification regulations and guidance memorandum. However, FDA's guidance requires some clarification to make it internally consistent. Because of FDA's inadequate documentation of the review process, GAO could not determine whether FDA's decisions are made in accordance with its stated policy. GAO also found significant weaknesses in the implementation of other provisions of the amendments that affect premarket notification.

Principal Findings

Policies Governing Premarket Notification Are Generally Adequate

FDA issued written guidance for determining substantial equivalence in 1986. While the guidance is generally adequate and consistent with the less restrictive reading of the legislative history, the description of how reviewers should assess the effect of a change in a device on its performance contains some ambiguities. GAO also found differences among the reviewing divisions within the Office of Device Evaluation concerning when to request additional information from the manufacturer, which further suggests a lack of clear office-wide policy and of coordination among the divisions. (See pages 49 to 51 and 70 to 74.)

Documentation Needs to Be Improved

In reviewing over 1,000 premarket notifications, GAO found that almost all files included a standard form containing the recommended decision and the concurring signatures of the branch chief and division director. However, documentation of the questions raised during review and of the reasons for review decisions varied depending on the review decision. While there is fuller documentation of difficult decisions, the documentation is inadequate to evaluate the extent to which formal review policy is being implemented consistently across decisions. FDA recognizes

that better documentation is needed and is devising a plan for improvement in this area. (See pages 67 to 68.)

Implementation Failures Have Implications for Premarket Notification

FDA has called for premarket approval applications for only 9 of approximately 150 types of preamendment class III devices. In addition, no performance standards for class II devices have been completed. Furthermore, publication of the final classification regulations for all types of medical devices has only been completed over the last two years. Because of these implementation problems, devices in class II and class III may be marketed through premarket notification without having to meet the additional requirements appropriate to their classification. As a result, FDA must place more reliance on premarket notification to control access of medical devices to the market than would otherwise be the case.

The amendments do not specify a deadline for implementing the performance standards and premarket approval provisions. In addition, some experts have questioned the need for developing performance standards for all class II devices. Nevertheless, GAO believes that developing no performance standards at all, and requiring premarket approval applications for only 9 of 150 types of class III devices in the first eleven years of the program, represent inadequate progress. GAO also recognizes that these activities are resource intensive. FDA estimates that it takes 1,200 hours to review each premarket approval application and 40 staff years to develop a single standard. Only in late 1987 was a long-standing backlog of premarket approval applications eliminated. If FDA is to make more rapid progress in developing performance standards and reviewing premarket approval applications for preamendment devices, additional resources will be required.

Relying on Pre-1976 Devices for Determining Substantial Equivalence Is Problematic

The amendments require that substantial equivalence determinations be made relative either to devices that were in commercial distribution prior to the amendments or to reclassified post-1976 devices. If manufacturers can demonstrate that their devices are used for the same purposes and perform as well as products marketed prior to 1976, FDA must now find the products to be substantially equivalent even if there are other products already on the market that "work better." If the comparison were made to a currently marketed device, FDA could presumably find a new device not substantially equivalent, even in the absence of performance standards, if it were not equally safe and effective.

Recommendations

Recommendation to the Congress and Matter for Congressional Consideration

GAO recommends that the Congress amend the Federal Food, Drug and Cosmetic Act to require FDA to determine substantial equivalence based on a comparison with a currently marketed device, rather than a pre-1976 device. (Proposed legislative language is on page 53.)

In light of the problems in implementing parts of the amendments, the Congress may also want to consider (1) clarifying the extent to which FDA should evaluate, within the premarket notification process, the effects of changes in medical devices on their safety and effectiveness; and (2) developing alternative approaches to the regulation of devices currently placed in classes II and III that could accomplish the original purposes of the amendments. (See page 43.)

Recommendations to the Department of Health and Human Services (HHS)

GAO recommends that the secretary of HHS instruct the commissioner of FDA to require that written documentation of the review and decision-making process be included in each premarket notification file. The extent of documentation should vary according to the seriousness of the review questions raised. (See page 77.)

GAO also recommends that the secretary of HHS instruct the commissioner of FDA to develop and implement processes for identifying scientific issues that require uniform treatment across the divisions of the Office of Device Evaluation, for developing policies, and for ensuring that these policies are implemented consistently in the review of premarket notifications. (See page 79.)

Agency Comments

HHS provided official comments on an initial draft of this report, characterizing the report as thorough and fair and concurring with GAO's recommendations to the secretary of HHS. (See appendix VI.) The initial draft portrayed FDA's regulations and policies as generally consistent with the statute and legislative history. GAO subsequently decided that the legal status of the regulations and policies was not germane to the thrust of the report and therefore made appropriate revisions. The revisions do retain the observation that the regulations and policies adopted by FDA are consistent with a less restrictive reading of the legislative history. However, FDA found the revised draft to be less satisfactory than the original. (See pages 53 to 54.)

Contents

Figures

Abbreviations

FDA	Food and Drug Administration
FTE	Full-time equivalent
GAO	General Accounting Office
HHS	Department of Health and Human Services
ODE	Office of Device Evaluation (FDA)

Introduction

Background

Ever since the turn of the century, the Congress has consistently shown its concern for the protection of the public from the harmful effects of contaminated food and unsafe or ineffective drugs. In 1906, the Congress passed the Food and Drugs Act, which barred from interstate commerce any adulterated or misbranded foods or drugs. In 1938, it passed the legislation that serves as the basis for the current statute, the Federal Food, Drug, and Cosmetic Act (hereafter referred to as the act). The act required Food and Drug Administration (FDA) review of new drugs for safety prior to marketing and contained provisions to regulate cosmetics and medical devices for the first time. It did not require evidence of effectiveness for drugs, nor did it require FDA review of medical devices prior to marketing. At that time, the prevailing attitude in the Congress was that most medical devices were simple enough that defective devices could be easily identified by the user and that therefore they posed no danger to the public. The Congress did believe that these devices should be properly labeled and unadulterated, and the act included a section defining the term "device" and prohibiting misbranding and adulteration.

For the next thirty years, the FDA played mainly a policing role, prosecuting manufacturers who marketed devices that were fraudulently labeled or obviously adulterated. As time went on and medical science advanced, medical devices became more and more sophisticated, and defective devices were not so easily detected by their users. FDA realized that these sophisticated devices posed a potential danger to the public and thus needed to be reviewed before being put on the market. Under the act, FDA did not have the authority to conduct premarketing review of medical devices.[1] FDA's solution was simply to redefine these potentially hazardous devices as drugs. However, while successful in some cases, this was clearly not a long-term solution.

In an address to the Congress on October 30, 1969, President Nixon indicated that the government should become more involved in the regulation of medical devices as part of an overall plan to protect the interests of consumers. A study group on medical devices, later to become known as the Cooper Commission, was formed by the Department of Health, Education, and Welfare to examine the issue and make recommendations that would serve as the basis for a legislative proposal. Many of the Cooper Commission's recommendations are reflected in the Medical Device Amendments of 1976 (hereafter referred to as the amendments).

[1] We use the terms "premarket" and "premarketing" interchangeably throughout this report.

The Medical Device Amendments of 1976

Figure 1.1 on page 12 is a schematic representation of the various steps to be followed in getting a medical device onto the market, including the section of the amendments that governs each step. Each of these provisions is described briefly below and in more detail in chapter 2.

Definition of a "Device"

The term "device" is defined in section 201(h) of the amendments as

> "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is ... [either] intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals ... or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes."

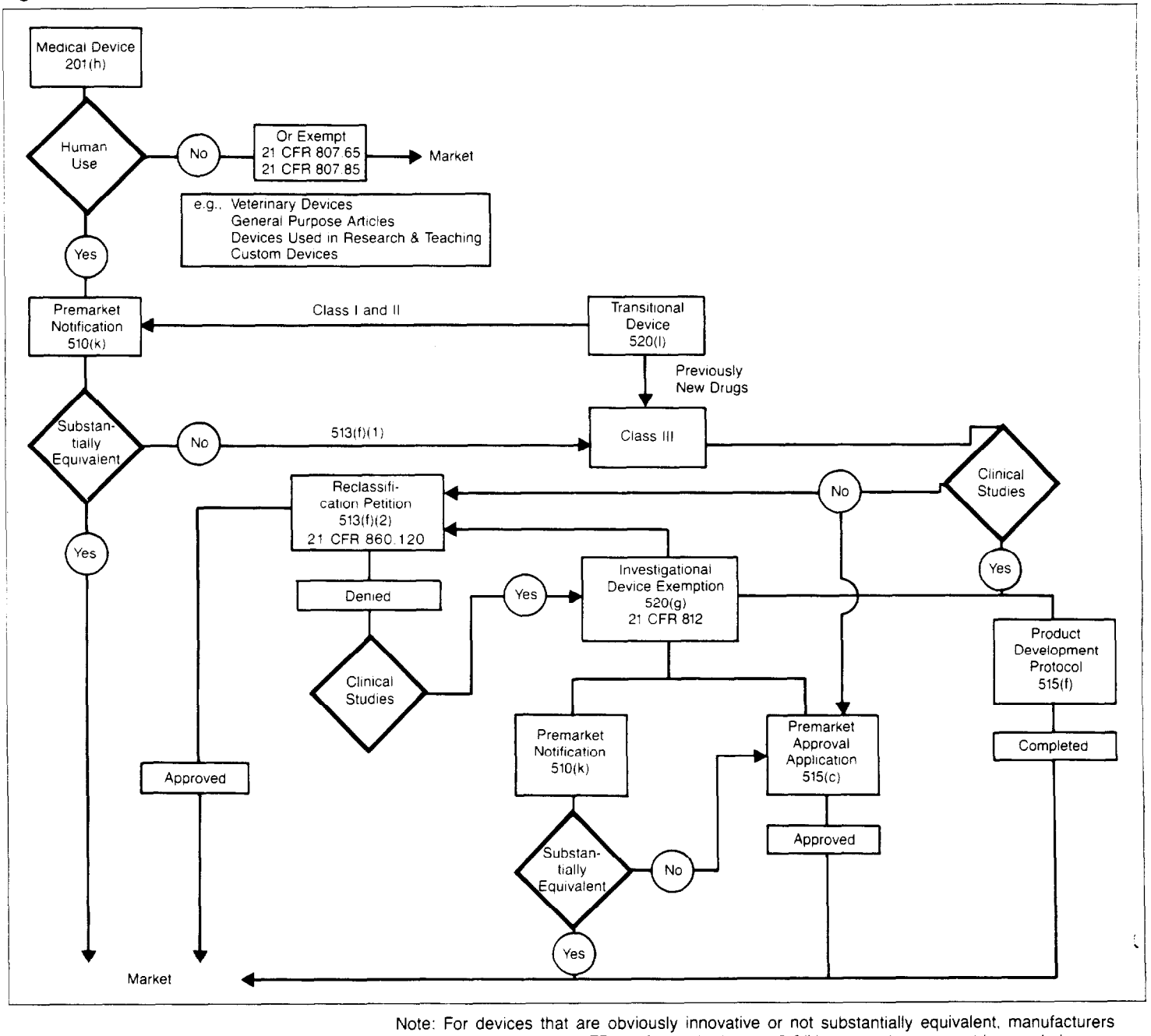
The definition is very broad. It could include almost any item for which claims are made of usefulness in promoting health or preventing or curing illness, provided that the mode of operation is not chemical or metabolic. Thus, for example, a mattress pad for which an advertising claim was made that it cured insomnia might be considered a device. Everything from tongue depressors and surgical gowns through lithotriptors and magnetic resonance imaging devices are regulated by FDA under this definition.

Classification of Devices

In drafting the amendments, the Congress was concerned with ensuring the safety and effectiveness of potentially hazardous devices while at the same time not unduly restricting development of innovative devices or improvements to existing devices. This meant that the premarketing review process would have to be rigorous enough to protect the public from hazardous or ineffective devices while at the same time not so cumbersome that it would discourage manufacturers from trying to market innovative products. In addition, since medical devices run the gamut from bandages and tongue depressors to magnetic resonance imagers and lasers, not all devices should be subject to the same level of regulation. Thus, a three-tiered system of classification and regulation was created.

Devices in class I (such as tongue depressors) are those for which general controls provide reasonable assurance of safety and effectiveness. Class II devices (such as hearing aids) require performance standards in

Figure 1.1: How to Get to Market With a Medical Device



Note: For devices that are obviously innovative or not substantially equivalent, manufacturers are urged to consult with FDA before submitting a 510(k), a step that may not be needed.

Source: U.S. Department of Health and Human Services, Food and Drug Administration, Regulatory Requirements for Medical Devices: A Workshop Manual, FDA 85-4165 (Washington, D.C.: U.S. Government Printing Office, 1985).

addition to general controls in order to provide such assurance. Devices placed in class III (such as pacemakers) are required to undergo premarket approval to be proven safe and effective as well as to comply with general controls. Finally, a formal process was specified for assigning devices to these three classes.

To facilitate the classification of devices, the Congress termed those devices regulated as drugs prior to the amendments "transitional devices" and placed them into class III. All other preamendment devices (that is, those on the market prior to the amendments) were to be placed in class I, class II, or class III by FDA, based on the recommendations of panels of experts. Postamendment devices were to be placed into one of the three classes based on their "substantial equivalence" to a "predicate" device (that is, either a preamendment device or a postamendment device reclassified into class I or II); devices found not substantially equivalent were automatically placed into class III. All devices could be moved from one class to another based on an approved reclassification petition.

Review of Devices Prior to Initial Marketing

The amendments prescribe two premarketing review processes. Premarket notification (also referred to as section 510(k)) was required of all postamendment devices and was to be used by FDA for identifying "new" devices based on a determination that the device was not "substantially equivalent" to a predicate device. The amendments automatically place such "new" devices into class III. Premarket approval was to be used for reviewing the safety and effectiveness of these "new" devices and of all other postamendment class III devices based on "well-controlled investigations" or other "valid scientific evidence." In practice, this requirement typically means that the manufacturer must conduct clinical trials of the device.

Prior Assessments of Implementation

Since 1976, there have been periodic assessments of FDA implementation of the amendments by the Congress and congressional agencies.[2] These investigations have mainly focused on FDA's pace and priorities in implementing the law and on alternatives for revising certain provisions of the law which have not worked as expected. The findings have been quite similar.

- FDA has classified many, but not all, of the 1,700 types of preamendment devices;
- FDA has not established the required performance standards for class II devices;
- FDA has done very little to bring preamendment (and substantially equivalent postamendment) class III devices under the premarket approval process and to evaluate their safety and effectiveness.

In 1987, the Hon. Henry Waxman and the Hon. John Dingell introduced H.R. 2595 which has several provisions affecting premarketing review of medical devices that are aimed at addressing the problems noted earlier. While our findings do have implications for changes in the amendments, we do not directly compare our findings to the proposed changes because the proposed legislation was still undergoing revisions at the time this report was written.

Objectives, Scope, and Methodology

Objectives

This study, requested by Representative Henry Waxman, Chairman of the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, examines FDA's administration of

[2]U.S. Congress, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, FDA Oversight: Medical Devices. Hearings: July 16, 1982, 98th Cong., 1st sess. (Washington, D.C.: U.S. Government Printing Office, 1982); U.S. Congress, House of Representatives, Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, Medical Device Regulation: The FDA's Neglected Child, An Oversight Report on FDA's Implementation of the Medical Device Amendments of 1976 (Washington, D.C.: U.S. Government Printing Office, 1983); U.S. General Accounting Office, Federal Regulation of Medical Devices--Problems Still to Be Overcome, GAO/HRD-83-53 (Washington, D.C.: September 1983); U.S. Congress, House of Representatives, Committee on Energy and Commerce, Subcommittee on Health and the Environment, Health and the Environment: Miscellaneous, Part A, Medical Device Amendments of 1976. Hearings: February 22, 1984, 98th Cong., 1st sess. (Washington, D.C., U.S. Government Printing Office, 1984); Office of Technology Assessment, Federal Policies and the Medical Device Industry. (Washington, D.C.: U.S. Government Printing Office, October 1984).

premarket notification, including the determination of substantial equivalence, taking into consideration both formal policies and day-to-day operations. We also examine FDA's implementation of other provisions of the amendments that have implications for premarket notification.

Scope

We reviewed the activities undertaken by FDA in the eleven years since the amendments were enacted. While some attention is given to early activities, such as the publication of initial regulations implementing the various legislative provisions, most of the report deals with the premarket notification function as it exists today. Our discussions with FDA officials were conducted between November 1986 and October 1987. We also reviewed a sample of premarket notifications received by FDA during calendar year 1986.

The report focuses on the implementation of the premarket notification provisions of the amendments. We examine the policies and procedures under which FDA reviews premarket notifications and makes determinations of substantial equivalence and compare them to implementation criteria developed from the statute and associated legislative history. We do not attempt to judge whether individual determinations of substantial equivalence are appropriate or inappropriate. We examine the types of information available to the reviewers, although we do not attempt to determine the completeness or validity of the information submitted to FDA by manufacturers. We did not obtain information on manufacturers' views of the program. Our review of the implementation of other provisions was less intensive and limited to those issues that have implications for premarket notification.

Methodology

Our study design involved three major lines of effort. First, a framework or set of criteria was developed based on the statute and its legislative history. These criteria were used to judge the degree to which FDA's implementation of the premarket notification and related provisions of the amendments is consistent with the statute and other indications of intent. Second, a review of FDA regulations and documents, combined with extensive interviews with FDA officials, provided information on FDA's implementation of the amendments in general and, in particular, on the policies, procedures, and day-to-day operation of the premarket notification program. Finally, a representative sample of premarket notifications submitted in 1986 was analyzed to develop evidence on the information contained in the files as well as on the review and decision-making process.

Our study was conducted in accordance with generally accepted government auditing standards.

Criteria Development

We made a substantial effort to develop criteria that reflected the statutory language and legislative history. In addition, a literature review was conducted that encompassed both early articles and reports on the regulation of medical devices and later articles that explicated the reasons for current criticisms of FDA's implementation of the amendments.

The results of our review were summarized in a working paper that presented our understanding of the system of premarketing activities implied by the various statutory provisions on three levels: general regulatory mechanisms, policies and procedures, and day-to-day operations. Comments were requested from reviewers selected for their knowledge of the amendments and the issues surrounding premarket notification. (See appendix I.) Some of these reviewers were involved either in the passage of the amendments or with FDA's implementation of them. The working paper provided us with a framework for judging the adequacy of FDA's implementation of the premarket notification and related provisions of the amendments.

Review of FDA's Implementation

We obtained and reviewed regulations and other policy-related FDA documents that concern premarket notification and related processes. We also obtained and analyzed data from an automated data base that contained information on all premarket notifications filed from 1976 to 1986. Total numbers, classification, decision, and calendar time to decision were examined.

We conducted extensive interviews with individuals at each level in the Office of Device Evaluation (ODE) within the Center for Devices and Radiological Health. We had meetings with the director, deputy director, and 510(k) coordinator regarding overall ODE policy, the structure of premarketing review, and the processing of premarket notifications. We conducted interviews with each of the seven ODE division directors to discuss their implementation of ODE policies and guidance and the management of the review process. Finally, we met with selected reviewers and branch chiefs in each of the seven divisions and discussed the decision-making process from their perspective and their day-to-day activities. In these meetings, we also discussed actual premarket notifications that these individuals had reviewed.

Analysis of a Sample of Premarket Notifications

We reviewed a random sample of over 1,000 premarket notifications submitted in calendar year 1986, stratified by the review decision and device class. (See appendix II for details.) The sample was designed to have a maximum sampling error of ± 6 percent in any stratum. Data were abstracted from the microfiche records of the individual premarket notifications. We examined the types of information contained in the original submission, the types of additional information requested by FDA, and the supplemental information actually provided by manufacturers. (See appendix III.) The decision itself and information about the extent of documentation were also abstracted.

Report Organization

In chapter 2, we present the statutory requirements of the premarket notification and related provisions of the amendments and evaluate, at a structural level, the extent to which FDA has implemented each of them. We discuss the effects that failure to implement certain provisions of the amendments have on premarket notification. In chapter 3, we discuss FDA policies that govern the determination of substantial equivalence.

In chapter 4, we evaluate the extent to which what actually happens in the day-to-day operation of the premarket notification program matches the formal policy. We review how notifications are processed and decisions made, and describe both the information provided to FDA and what additional information FDA requests and receives. We judge the extent to which the process is consistent with the statute and legislative history, using the criteria discussed above. Finally, we address two specific criticisms of the process: that too many medical devices reviewed in the premarket notification process are found to be substantially equivalent and that FDA is conducting "mini-PMAs" (that is, mini-premarket approvals) as part of premarket notification.

The Implementation of Premarketing Review of Medical Devices: Regulatory Mechanisms

In this chapter, the requirements of the amendments concerning premarketing review and their implementing regulations are presented. Our analyses are primarily structural and are based on two questions: are the required mechanisms in place, and do they relate to each other in the specified ways?

The chapter begins with a discussion of premarket notification—the provision that is the primary focus of this review. We examine classification, reclassification, performance standards, and premarket approval in the sections that follow. In each section, we present the statutory requirements, FDA's implementation, and summary and implications. Finally, we present some information on the relationship of premarket notification to postmarketing compliance activities.

Most Postamendment Devices Are Marketed Through Premarket Notification

Section 510(k) of the act, the premarket notification provision, provides a mechanism for informing FDA of a manufacturer's intent to market a new or modified device, providing FDA with the manufacturer's judgment about the appropriate classification of the device pursuant to section 513 and describing actions taken to comply with sections 514 (performance standards) and 515 (premarket approval) of the amendments. However, FDA's inclusion of determinations of substantial equivalence based on section 513(f)(1), and the resulting classification of the device, extend the significance of premarket notification. In addition, if there were performance standards to enforce, FDA could review the performance of class II devices prior to marketing against the applicable performance standards as part of premarket notification.

Statutory Requirements

Premarket Notification

Premarket notification is one of the two procedures that FDA has for reviewing a medical device prior to marketing. Section 510(k) of the amendments contains three requirements. First, manufacturers must notify FDA at least ninety days before marketing a "new" device. Second, manufacturers must provide their preliminary judgment of the class that a device belongs in (or the lack of such a classification) and the basis for that assessment. This means that manufacturers must keep informed of FDA regulatory activities regarding the classification of the devices that they produce or market. Finally, manufacturers must

describe the actions they have taken to comply with the applicable performance standard (section 514) or premarket approval (section 515) provisions of the amendments.

The amendments also require FDA to issue regulations specifying the form and manner in which manufacturers must report to FDA. Section 510(k) does not explicitly require FDA to review the manufacturer's judgment concerning the classification of the device. Nor does it require the manufacturer to refrain from marketing for more than 90 days if FDA has not made a determination. However, the requirement to notify FDA suggests that FDA should take some responsibility for reviewing the initial judgments made by manufacturers concerning the class into which a new device falls. And, as will be elaborated upon in the next section, the legislative history of the amendments clearly indicates that FDA has the responsibility to make sure that "new" devices are not marketed until all applicable provisions of the statute have been satisfied.

Determination of Substantial Equivalence

Section 513(f)(1) provides that postamendment devices are to be automatically placed in class III unless they meet certain criteria. Postamendment devices are placed in class III unless they are "within a type of device" that was on the market prior to the amendments or that has been reclassified into class I or class II.[1] In addition, the "new" device must be substantially equivalent to a device within that type.

No administrative procedure is described for when and how determinations of substantial equivalence are to be made. However, with regard to when the determinations should be made, the legislative history makes it clear that the Congress provided the notification function in section 510(k) for the express purpose of providing FDA with an opportunity for reviewing postamendment devices prior to their initial marketing.

"The proposed bill contains provisions designed to insure that manufacturers do not intentionally or unintentionally circumvent the automatic classification of 'new' devices. These provisions, included in amendments to section 510 of the act, would require all persons to advise the Secretary ninety days before they intend to begin marketing a device as to whether the device has been classified under section 513.

[1]The term "device" is used to refer to a particular device produced by a manufacturer. A "type" of device is the generic category into which a particular device falls. For example, implantable pacemakers are a device type; several different manufacturers make pacemaker "devices" that are more or less equivalent. However, in order to simplify the presentation here, the term "device" typically will refer to the "type of device" rather than to any particular manufacturer's product.

This provision will enable the Secretary to assure that 'new' devices are not marketed until they comply with premarket approval requirements or are reclassified into class I or II."[2] [Emphasis added.]

It is clear from this passage that the Congress intended that FDA would make the determination prior to marketing so that "new" devices would be identified, placed in class III, and obtain premarket approval before being used by the public.

Concerning how the determination should be made, the statute does not define substantial equivalence. The pertinent house report, which is the only part of the legislative history that addresses this matter, contains the following discussion:

"The term 'substantially equivalent' is not intended to be so narrow as to refer only to devices that are identical to marketed devices nor so broad as to refer to devices which are intended to be used for the same purposes as marketed products. The Committee believes that the term should be construed narrowly where necessary to assure the safety and effectiveness of a device but not so narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness. Thus, differences between 'new' and marketed devices in materials, design, or energy sources, for example, would have a bearing on the adequacy of information as to a new device's safety and effectiveness, and such devices should be automatically classified into class III. On the other hand, copies of devices marketed prior to enactment, or devices whose variations are immaterial to safety and effectiveness would not necessarily fall under the automatic classification scheme."[3]

As noted below, this passage is subject to differing interpretations. However, a number of the important elements of a determination of substantial equivalence are clearly stated here. First, a "new" device need not be identical in all respects to a predicate device in order to be considered substantially equivalent. Second, if the only connection between a "new" device and a predicate device is that they have the same intended use, that is not sufficient to find them substantially equivalent. Some greater degree of equivalence is required. Finally, the passage suggests that equivalence should be construed narrowly where differences between devices could affect safety and effectiveness but more broadly where the changes do not affect safety and effectiveness.

[2]U.S. Congress, House of Representatives, The Medical Device Amendments of 1976, House Report No. 94-853, 94th Cong., 2nd sess., (Washington, D.C.: U.S. Government Printing Office, 1976), p. 37. (We refer to this document as the house report.) The Congress adopted the premarket notification provision as originally proposed in the House.

[3]House report, pp. 36-37.

The house report language is not clear about which differences between devices relate to safety and effectiveness. According to one reading, any difference between a "new" device and a predicate device in materials, design, or energy sources would materially affect safety and effectiveness and thus should result in a "not substantially equivalent" decision, automatically causing the device to be placed in class III. Under a less restrictive reading of the passage, only those changes that could, or do, materially affect safety and effectiveness should result in a "not substantially equivalent" decision. As noted in later sections of the report, FDA's actions are consistent with the less restrictive reading of the House Report guidance.

Compliance With Performance Standards

Section 510(k) requires that the manufacturer describe actions taken to comply with section 514 (performance standards). We believe that FDA has the authority to request and review any information necessary to assure that the device meets the applicable performance standard. FDA could accept at face value the manufacturers' statement of compliance or, arguably, it could require that the results of complete and thorough testing be submitted to substantiate claims.

Implementation

The Implementing Regulation

In August 1977, FDA published final regulations (42 Fed. Reg. 42520; codified at 21 C.F.R. 807) implementing section 510(k) of the statute. The regulations as well as the policies that are implied by FDA's responses to the comments on the proposed regulation have remained essentially unchanged. The regulations specify what situations require submission of a premarket notification, what types of information should be submitted, and where it should be sent. In particular, FDA outlines the types of situations in which premarket notification for device modifications would be required, most notably for "changes that could significantly affect safety and effectiveness" and for "major change or modification in the intended use of the device." Class III devices with pending premarket approval applications were not required to have separate premarket notifications.

FDA also makes it clear that they intend actively to make determinations of substantial equivalence as part of the premarket notification process. The commissioner of FDA retains the right to ask for any additional

information necessary to make a determination of substantial equivalence. Further, if the additional information is not submitted within thirty days following the date of the request, FDA considers the premarket notification withdrawn. The regulations contain no mention of the role premarket notification might play in the review of devices for compliance with performance standards.

These regulatory requirements, combined with the postmarketing tools FDA has for removing devices from the market (such as seizure and recall), effectively induce most manufacturers to refrain from marketing until a finding of substantial equivalence is made. That is, if a premarket notification is considered withdrawn by FDA because the manufacturer did not respond to a request for information, and a manufacturer then decides to market the device anyway, FDA regards the device as "misbranded" under the amendments and therefore subject to recall. If FDA decides that the device is not substantially equivalent and the device is marketed anyway, the device is regarded as "adulterated" under the amendments because it does not have an approved premarket approval application, and thus is subject to recall. Violations of the requirements of section 510(k) were cited in 20 percent of regulatory letters issued by FDA between January 1985 and August 1986.[4]

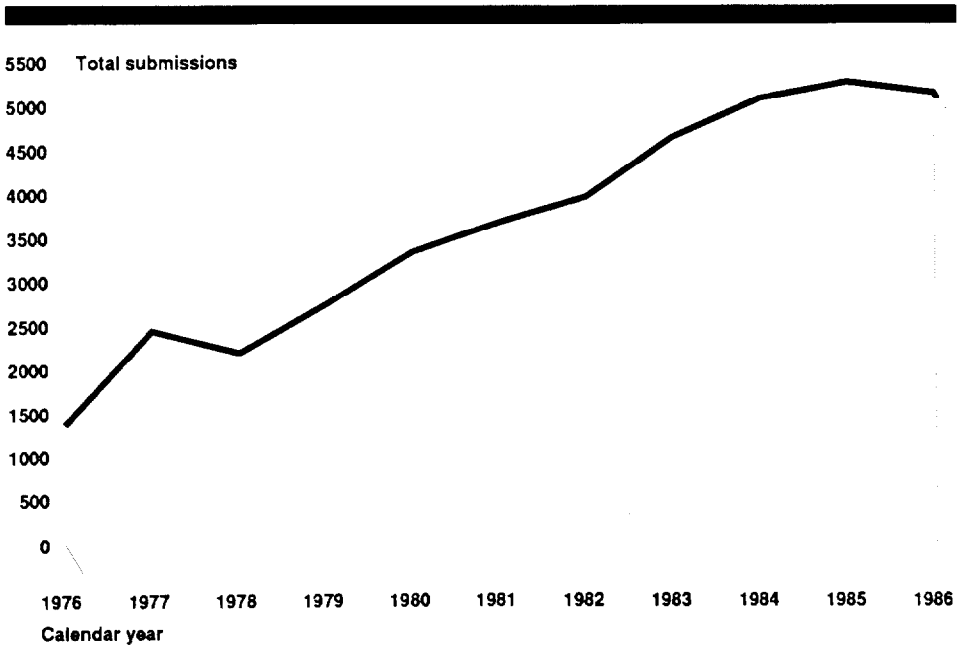
There was, and still is, some disagreement about the nature and extent of the premarket notification regulations. For example, some attorneys argue that premarket notification is a simple notification provision and that FDA has overreached its authority by requiring sufficient information in a premarket notification to make a determination of substantial equivalence. Others believe that FDA has responded reasonably. No court decisions have challenged FDA's authority to prevent the marketing of a device prior to their making a substantial equivalence determination.

Program Statistics, 1976-1986

In the first eleven years of the program, almost 40,000 premarket notifications were processed by FDA. The annual number of applications increased steadily through 1985 and now appear to be leveling off at slightly more than 5,000 per year. (See figure 2.1 on page 23.)

[4]J. Gibbs, "Medical Devices and Regulatory Letters: An Analysis of FDA Enforcement Actions," Medical Device and Diagnostics Industry, August 1987.

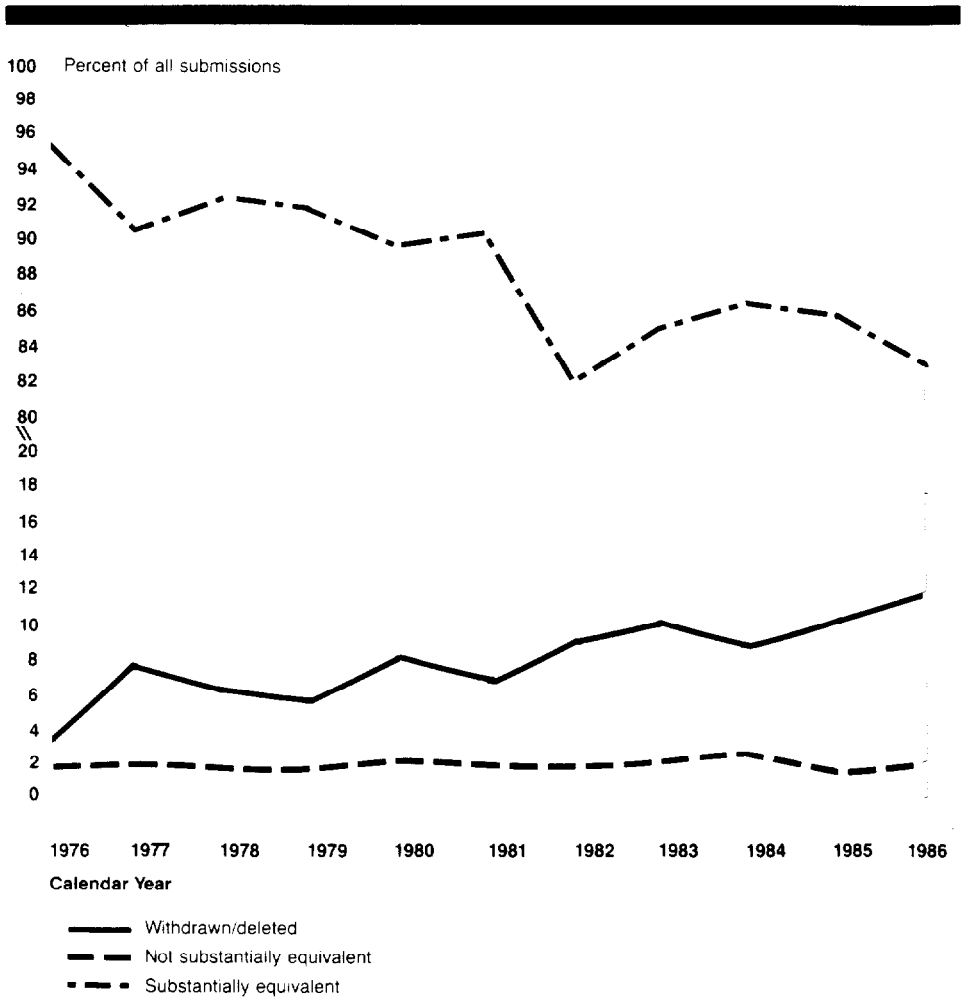
Figure 2.1: Number of Premarket Notifications, 1976-1986



The percent of all premarket notifications found substantially equivalent held steady at around 90 percent from 1977 through 1981. (See figure 2.2 on page 24.) It dropped to around 85 percent over the next few years, coincident with the period of time during which the Congress was conducting oversight hearings critical of FDA's implementation of the amendments. The percent of notifications found substantially equivalent then remained steady at about 84 to 86 percent through 1986. In total, over 34,000 notifications were found substantially equivalent between 1976 and 1986. The percent of notifications found not substantially equivalent remained fairly constant at around 2 percent over the entire period. The percent of withdrawn and deleted applications rose from 7 percent in 1977 to almost 11 percent in 1986.

Figure 2.3 on page 25 shows changes over time in the percent of notifications falling into each of the three regulatory classes as well as the percent for which the classification is missing. The percent of devices falling into class I and class III has remained relatively constant over time. The percent of devices placed in class II dropped from around 55 percent before 1981 to around 48 percent from 1982 to 1986. The percent of devices for which the classification designation is missing increased from around 12 percent prior to 1981 to over 20 percent from 1982 to 1986.

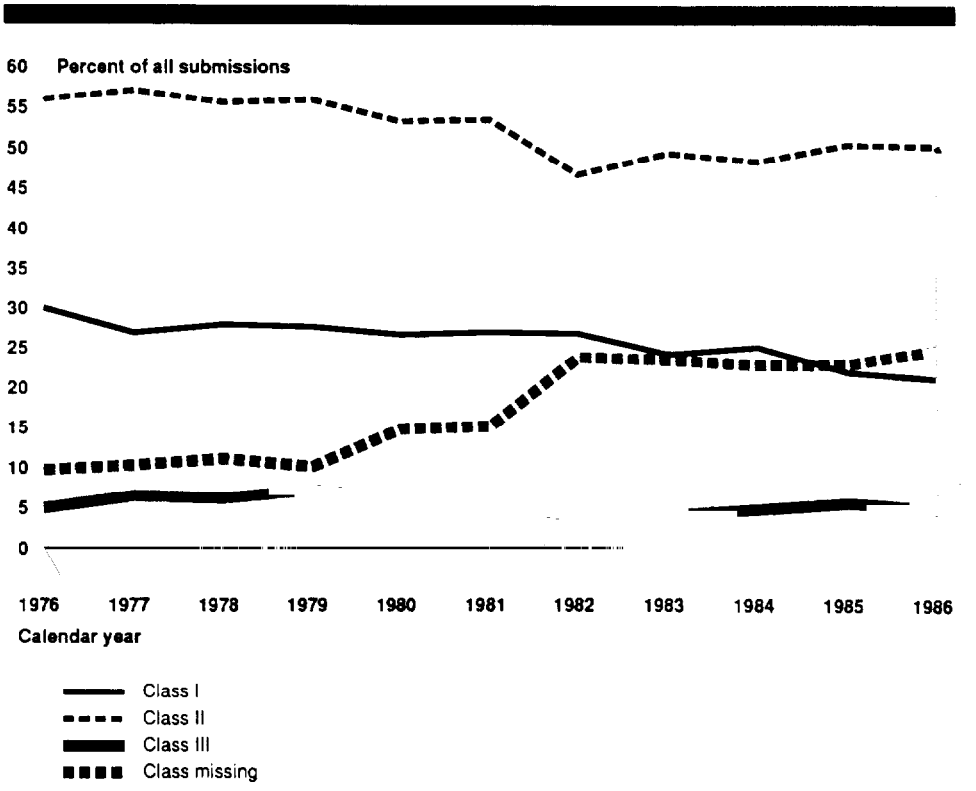
Figure 2.2: Percent of Premarket Notifications by Decision, 1976-1986



The classification of a device will be missing from FDA's data base if a product code was not assigned during the review process or the assigned product code did not match a record in FDA's classification file.[5] The underlying reasons for this situation included data entry errors, reviewers using "ZZZ" as a generic product code when they were not certain of the appropriate code, withdrawn and deleted notifications not being classified, devices found not substantially equivalent, as well as truly

[5]Three-letter product codes are associated with each of the types of preamendment devices. The reviewer of a premarket notification is supposed to record the product code of the predicate device to which the "new" device is being found substantially equivalent.

Figure 2.3: Percent of Premarket Notifications by Class of Device, 1976-1986



unclassified devices.[6] FDA is aware of this data problem and is working to correct it.

Summary and Conclusions

While some have argued that premarket notification is a simple notification provision and should not be linked with the classification of postamendment devices through determinations of substantial equivalence, we believe that the legislative history, as embodied in the house report, clearly indicates that they are related. As a result, FDA's decision to make determinations of substantial equivalence based on information submitted under section 510(k) is consistent with the statute. The evaluation of new class II devices against applicable performance standards could also be implemented as part of the premarket notification program but has not been, due to the lack of performance standards.

[6]Approximately one-third of the notifications for which the classification is missing represent notifications that have been withdrawn or deleted prior to the issuance of a decision. Thus, much of the increase in the percent of notifications with missing classifications can be explained by the increase in the percentage of notifications that are withdrawn or deleted.

At this structural level of analysis, we find that FDA's implementation of the premarket notification program is consistent with the less restrictive reading of the house report. Over time, large numbers of premarket notifications have been processed. However, when the number of devices and device modifications marketed through premarket notification (roughly 34,000) is compared with that marketed through premarket approval (roughly 2,200; see page 37), the obvious conclusion to be drawn is that the program may have taken on an importance beyond that envisioned by the Congress. (We will examine the premarket notification program in greater detail in chapters 3 and 4.)

Classification of Preamendment Devices Only Recently Completed

The appropriateness of the classification of preamendment devices is outside the scope of this study. However, the class to which a preamendment device is assigned determines the level of review that is required (that is, premarket notification or premarket approval) and the postmarketing regulatory controls that will be exercised. It also serves as the basis for the automatic classification of postamendment devices based on a determination of substantial equivalence. Finally, premarket approval for devices placed in class III cannot commence until at least 30 months after the publication of the final classification regulation for that category of devices.

Statutory Requirements

The Classification System

The amendments established a system with three classes of medical devices. Class I devices are those for which general controls are considered sufficient to provide reasonable assurance of the safety and effectiveness of the device. General controls include, among others, prohibitions against adulteration and misbranding and a set of regulations governing good manufacturing practices. Tongue depressors, ice bags, and bed pans are examples of class I devices.

Class II devices are those for which general controls are insufficient to provide reasonable assurance of safety and effectiveness and about which there is enough information to establish a performance standard. Class II devices must also comply with the general controls governing class I devices. Syringes, hearing aids, and resuscitators are examples of class II devices.

Class III devices are those for which information is not sufficient to determine whether general controls, performance standards, or both would provide reasonable assurance of safety and effectiveness and which are intended to be used for supporting or sustaining human life, are substantially important for preventing the impairment of health, or present a potentially unreasonable risk of illness or injury. Class III devices are subject to the premarket approval process in which the manufacturer has to present evidence, including extensive clinical data, that the device is safe and effective before placing it on the market. Class III devices are also subject to general controls. Heart valves, pacemakers, and infant radiant warmers are examples of class III devices.

Transitional Devices

Prior to the passage of the amendments, FDA recognized the need to review certain products for safety and effectiveness before they went on the market. This group of products included sutures, injectable silicone, intraocular lenses, and soft contact lenses. In the amendments, the Congress recognized the special status of these products by enacting "transitional provisions" that placed them in class III and covered their transfer from regulation as drug products to regulation as devices (section 520 (l)). Furthermore, any new device found to be "substantially equivalent" to a transitional device must also be placed in class III and go through the premarket approval process.

Preamendment Devices

The amendments established a procedure for placing the roughly 1,700 types of nontransitional devices existing prior to the 1976 amendments into one of the three classes. The amendments required FDA to set up panels of experts in each medical specialty. These panels were required to review the available information on each type of device and make recommendations to FDA on their appropriate classification. The deadline for the completion of the panels' work was to be one year after the funds were appropriated for this activity. After receiving the recommendations of the classification panels, the commissioner of FDA had to develop a proposed classification regulation and publish it in the Federal Register. Interested persons then would have the opportunity to react and provide comments. After reviewing all comments, the commissioner would develop and publish a final classification regulation. No timetable is specified by the amendments for completion of this part of the classification process.

Implementation

Transitional Devices

A notice was published in the Federal Register on December 8, 1977, that described FDA's policy regarding the implementation of the provisions of the amendments relating to transitional devices. The notice specified how FDA would manage the review of applications from manufacturers of new or modified transitional devices and how manufacturers could apply for reclassification of their devices. It also contained a list of products that FDA would regulate as transitional devices and a separate list of products that would be classified into class I or class II along with other preamendment devices. Some of the products on this second list included gauze bandages, adhesive tape, tampons, and dental adhesives.

From 1977 through 1982, transitional devices accounted for 59 percent of the 128 Class III products that were granted premarket approval. Most of these applications were for ophthalmic products, including contact lenses and related cleaning solutions, storage cases, and the like. Today, all premarket approval applications for transitional devices are reviewed by the Office of Device Evaluation. Transitional products, most notably contact lenses, have been the subject of reclassification petitions that were denied. However, in 1986, a petition to reclassify one type of transitional device, stainless steel sutures, into class II was approved.

Preamendment Devices

Based on the recommendation of the Cooper Commission, FDA had already begun the process of classifying medical devices by dividing devices into fourteen separate categories to be assessed by fourteen advisory panels. These categories were revised slightly, and the panels were officially established by Federal Register notice on August 25, 1976. Procedures for developing final classification regulations were adopted on July 28, 1978. As table 2.1 shows, proposed regulations specifying device classifications in each of the 19 specialty areas had been published by July 1982.

Table 2.1: Classification Regulation Publication Dates

Medical specialty	Regulation		Device types
	Proposed	Final	
Neurology	11/28/78	9/04/79	101
Cardiovascular	3/09/79	2/05/80	138
Obstetrics and gynecology	4/03/79	2/26/80	69
Hematology and pathology	9/11/79	9/12/80	109
General hospital and personal use	8/24/79	10/21/80	94
Anesthesiology	11/02/79	7/16/82	134
Immunology and microbiology	4/22/80	11/09/82	162
Physical medicine	8/28/79	11/23/83	81
Gastroenterology and urology	1/23/81	11/23/83	56
Ear, nose, and throat	1/22/82	11/06/86	67
Clinical chemistry and clinical toxicology	2/02/82	5/01/87	206
Dental	12/30/80	8/12/87	185
Orthopedics	7/02/82	9/04/87	77
Ophthalmology	1/26/82	9/02/87	119
Radiology	1/29/82	1/20/88	73
General and plastic surgery	1/19/82	6/24/88	54
Total			**1,725**

However, the publication of final regulations has been considerably slower. While the first group of final regulations took less than a year to complete, the final regulations for clinical chemistry and toxicology, published in May 1987, took over five years from proposed to final regulation. The remaining five final regulations were published over the next twelve months.

Based on either final or proposed regulations, roughly 54 percent of preamendment devices have been classified into class II. Class I devices represent about 35 percent of the total; class III devices represent 8 percent. Based on the past ten years' experience, FDA expects to reclassify many types of devices after all the classification regulations are final. It anticipates that as much as 45 to 50 percent of device types will eventually be placed in class I. In fact, in the final regulations published in fiscal year 1987, FDA shifted a number of devices originally proposed for class II into class I.

Summary and Implications

The classification of preamendment and transitional devices was begun in a timely fashion. The classification panels completed their work relatively quickly, and many of the proposed and final classification regulations were published in a relatively short period of time. The implementation of the provision of the amendments related to transitional devices was also completed in a reasonable period of time.

Conversely, the publication of the final classification regulations for seven of the medical specialty areas was delayed for several years. We did not examine why the process has taken this long. Part of the reason may be that FDA now feels that more devices should be placed in class I than were originally proposed. Ten years of experience have led to a recognition that the controls associated with class I provide a better assurance of safety and effectiveness than FDA originally believed.

Whatever the reason, however, there are important implications of this delay in completing the process. Until the proposed classification regulation for a category of preamendment devices (such as radiology devices) becomes final, FDA legally has not determined the class of any individual device in that category and therefore cannot apply any of the regulatory controls that may be appropriate to the device, beyond the general controls to which all three classes are subject. For example, the statute provides that manufacturers of devices placed in Class III by final regulation have a minimum of 30 months plus 90 days to file premarket approval applications. (This means that FDA cannot call for applications for at least 30 months, and manufacturers then have 90 days to file.) The clock does not start until the classification regulation becomes final. Further, devices proposed for class II cannot be required to meet performance standards until the classification regulation becomes final.

Reclassification Used Infrequently

Statutory Requirements

Procedurally, a reclassification proceeding is the mechanism by which the class of a device may be changed. Reclassification is addressed in five separate provisions of the amendments. While the exact procedural details vary in each case, FDA must decide, on the basis of publicly available information or information submitted by the petitioner, whether the controls of the proposed class will provide adequate assurance of

safety and effectiveness. (Proprietary safety-and-effectiveness data from premarket approval applications cannot be used by FDA without being released by the manufacturer.) In most cases, the consideration of a reclassification petition involves review by the appropriate classification panel and publication of a proposed regulation prior to making the reclassification final.

Either the manufacturer or FDA may initiate a reclassification proceeding based on new information bearing on the appropriate classification of the device for preamendment devices (section 513(e)) or postamendment devices found substantially equivalent through premarket notification (section 513(e)). When initiating either performance standard development (section 514) or a call for premarket approval applications under section 515(b), FDA must provide an opportunity for an interested party to ask for reclassification. Finally, in the case of a transitional device (section 520(l)) or a device found not substantially equivalent (section 513(f)(2)), the manufacturer must initiate the reclassification action.

Implementation

In practice, reclassification petitions have been limited almost exclusively to class III devices. In the past, FDA has strictly interpreted the evidence needed to support reclassification. Essentially, FDA required a demonstration of safety and effectiveness similar to that of a premarket approval, as well as a demonstration that the controls of the proposed class would provide reasonable assurance of safety and effectiveness. This required manufacturers who wanted to have their class III device reclassified into a lower class to provide FDA with almost as much information as would be required to gain approval of a premarket approval application. The manufacturers would either have to develop that data themselves or use publicly available data. Few manufacturers who have incurred the costs of developing data sufficient to have a premarket approval application approved would want to make those data available so that another manufacturer could market a similar device through the less costly premarket notification process.

FDA has also required that the formal administrative procedure detailed in section 513 (f)(2) of the amendments be followed for all reclassification petitions. That procedure may take up to 210 days from the time FDA determines that it has "complete" information on which to make a decision. On its face, the procedure is very similar to that used by the original classification panels in considering preamendment devices. It includes a panel review and recommendation, with publication of the

panel's recommendation in the Federal Register for public comment. FDA's final decision is in the form of an order (conveyed in a letter to the manufacturer) which is announced by a notice in the Federal Register.

Relatively few reclassification petitions have been filed since the amendments were passed. At the time of our last report on medical devices in 1986, only 39 petitions had been filed; 33 of those petitions had been approved.[7] Since that time, reclassification petitions have been filed for a number of devices, including stainless steel sutures, argon lasers for otology, neodymium, yttrium, aluminum garnet, lasers for posterior capsulotomy, infant radiant warmers, and magnetic resonance imagers. At this time, only stainless steel sutures have been reclassified. In addition, the recently published final classification regulation for ear, nose, and throat devices placed argon lasers for otology (but not those for other ear, nose, and throat conditions) in class II rather than class III.

Summary and Implications

The requirements for reclassification are stringent, resource intensive, and time-consuming, at least as FDA has implemented them to date. The data required are extensive, the appropriate panel must meet and consider the petition, and FDA must develop and finalize the necessary regulation. In addition, manufacturers who have already incurred the costs associated with approved premarket approval applications have strong financial incentives to closely guard their data and to oppose reclassification. As the result of an internal task force report, however, FDA is considering a reinterpretation of the statute that would result in a relaxation of the requirement that the device essentially be shown to be safe and effective before reclassification can be considered.

[7]U.S General Accounting Office, Medical Devices: Early Warning of Problems Is Hampered by Severe Underreporting, GAO/PEMD-87-1 (Washington, D.C.: December 1986), p. 32.

No Formal Performance Standards Yet Developed for Class II Devices

Statutory Requirements

The amendments require a performance standard for each type of class II device. The procedure for developing performance standards as well as the types of standards that could be imposed are detailed in section 514 of the act. As with classification and reclassification, the administrative work associated with the development (and subsequent periodic updating to reflect changes in technology and performance) of a performance standard is resource intensive and time-consuming. In addition, resources must be devoted to enforcing performance standards that have been developed.

Implementation

No formal performance standards have yet been developed under the procedures detailed in the Medical Device Amendments of 1976. Despite several attempts to initiate standards development in the past, none has gotten very far. However, a contract to begin the development of a standard for apnea monitors was recently announced. (The failure to develop performance standards has resulted in class II devices under premarketing review being treated in the same manner as class I devices.)

The development of performance standards for all current class II devices would require many years of effort. Given the over 1,000 types of devices currently in class II, an FDA official recently estimated that it would take 50,000 staff years to complete the task of developing performance standards. While we have not attempted to verify this particular estimate, it is consistent with past FDA estimates as well as with the experience of other Federal agencies.[8]

[8]In a previous report (GAO/HRD-83-53), we reported that FDA's former Bureau of Radiological Health took three years, at a cost of 40 staff years, to develop a standard. Other Federal agencies, including the Environmental Protection Agency and the Consumer Product Safety Commission, required from 2 to 5.5 years to develop a standard. Given that more than 1,000 types of devices require standards, an estimate of 50,000 staff years does not seem unreasonable.

In part as a substitute for performance standards, and in part as a guide to manufacturers and reviewers, FDA has informally adopted and uses a variety of voluntary standards, draft guidance, and other mechanisms against which to judge the design and performance of medical devices. Some of these voluntary standards were developed and endorsed by groups such as the Association for the Advancement of Medical Instrumentation, often with FDA assistance. In addition, FDA staff develops its own "guidance" documents for internal use. For example, FDA has a "draft guidance" that requires detailed testing data for ultrasound probes and sets maximum sound levels for particular diagnostic uses based on performance data from preamendment devices. Furthermore, FDA has indicated to manufacturers that a manufacturer not providing the "suggested" information or exceeding these standards would face a difficult, if not impossible, task in bringing its ultrasound probe to market.

In addition, FDA inspects facilities manufacturing class II and class III devices more frequently and gives these devices higher priority in other regulatory actions. The agency also develops educational programs aimed at solving use-related problems, "safety alerts" targeted at reported problems, and labeling guidance intended to enhance safe and effective use.

Although these approaches have benefits in terms of assuring a certain level of performance, there is no way to determine whether these informal standards are more or less stringent than a formal performance standard would be. Resources are required to develop such guidance; to date, the daily workload of reviewing applications has taken priority. In practical terms, FDA becomes bound by this guidance until it is revised and may not have the resources to revise it on a timely basis to reflect changes in technology or experience.

Summary and Implications

The failure to develop any performance standards is not consistent with the statute. One consequence of this absence of performance standards is that class II devices are subject only to general controls applicable to all three classes of devices. Conversely, the formal development of performance standards (and periodic updating) would be very resource-intensive and, according to many experts, not necessary for many class

II devices.[9] In addition, FDA would have to devote resources to enforcing compliance with any standards that are developed.

If the development of performance standards is still considered essential by the Congress, some approach to reducing the overall resources and time required for their development and approval is needed. For example, it seems to us that incorporating acceptable voluntary standards into formal performance standards would reduce the overall cost of developing standards. A simplified administrative procedure for the development and review of standards would help reduce the total cost. The reclassification of some low-risk class II devices into class I, something FDA has already indicated it intends to do, will reduce the number of devices requiring standards.

Premarket Approval for Preamendment Class III Devices Proceeding Slowly

Statutory Requirements

Premarket approval is the procedure specified in section 515 of the act for reviewing class III medical devices prior to marketing. The approval of a premarket approval application indicates that the benefits derived from the device (that is, clinical utility or effectiveness) have been shown to outweigh the risks associated with its use. The manufacturer must demonstrate, based on well-controlled investigations, that the device is safe and effective for its intended use in order to obtain premarket approval. The evidence presented by the manufacturer is reviewed by a panel of experts as well as by FDA. The public is also given an opportunity to comment on the application, although public access to the information is limited to a brief summary of the safety and effectiveness data. FDA is required to conduct the necessary meetings and reviews and make a decision within 180 days.

Under section 515, all class III devices (both preamendment and postamendment) are ultimately required to have premarket approval or be

[9]In our 1983 report, we stated that many experts felt that developing over 1,000 performance standards would be very time-consuming, expensive, and impracticable. At that time, we suggested that the Congress consider allowing FDA to determine, on a case by case basis, which class II devices require performance standards.

reclassified prior to marketing. Transitional devices and postamendment devices automatically classified in class III based on a "not-substantially-equivalent" determination were made subject to the requirements of section 515 upon its enactment. However, preamendment class III devices (and those postamendment devices found substantially equivalent to a preamendment class III device) can be marketed until FDA calls for applications for premarket approval.

As noted earlier, FDA is required to wait at least 30 months from the date of publication of the final classification regulation for a device before calling for applications and then must give manufacturers 90 days to submit applications. This is only the minimum time required; no maximum time limit is specified for initiating or completing the process. However, the legislative history indicates that the Congress set this period so that manufacturers would have the time necessary to develop information for a premarket approval application.

The legislation also provides FDA and the industry with two strategies for developing the information necessary to determine a device's safety and effectiveness, while at the same time protecting the rights of human subjects. The investigational device exemption is used to control the clinical testing of all devices, although FDA only formally reviews applications for "significant risk" devices.[10] The Product Development Protocol is an alternative to premarket approval whereby the manufacturer and FDA cooperatively develop a plan for testing a device. The successful completion of the Product Development Protocol, defined in terms of outcomes that demonstrate safety and effectiveness, constitutes approval to market the device.[11]

Implementation

A regulation implementing the premarket approval provisions of the amendments was proposed in 1980 but not made final until July 22,

[10]Clinical studies of other "nonsignificant risk" devices are reviewed and approved by institutional review boards and are subject to certain rules and record-keeping requirements. If the studies meet these requirements, they are deemed to have an approved investigational device exemption. FDA's Office of Device Evaluation receives approximately 200 new applications for investigational device exemptions each year.

[11]The Product Development Protocol, which was viewed in the house report as a way for manufacturers to work cooperatively with FDA to ensure that they would have the necessary data to demonstrate safety and effectiveness, has not been used for two important reasons. First, a company must provide sensitive commercial information to FDA and allow FDA an equal voice in designing the necessary studies. Second, and more important, a successfully completed Project Development Protocol becomes an "accepted" blueprint that other companies can follow in testing their products through the investigational-device-exemption process without incurring the costs of developing a testing protocol.

1986. The regulation establishes the procedures for premarket approval of medical devices. It also lays out the format and content of an application and sets forth the criteria that FDA will employ in making decisions on individual applications.

The final regulation contains some new guidance that was not part of the original proposed rule. First, under certain conditions, foreign data may be used as the sole basis of determining safety and effectiveness. This could increase the number of applications, although such an increase has not yet become evident. Second, supplements to premarket approval applications are now required for any change affecting the safety and effectiveness of the device, rather than just for changes that have a "significant" effect. Offsetting the expected increase in applications generated by this change is the development of a "30-day supplement" for reporting changes that clearly enhance the safety or use of the device. Under this provision, the manufacturer may make the change after 30 days unless FDA requests more information or responds unfavorably. Third, FDA made it clear that they want information in the premarket approval application on any important previous marketing of the device, on compliance with any applicable voluntary performance standards, and on any problems associated with clinical follow-up. Finally, the procedures for appealing an FDA decision that an application is incomplete and will not be formally reviewed have been clarified. While this will probably not result in a higher filing rate, there is now a more formal procedure by which a manufacturer can contest FDA's initial decision.

Available statistics on original premarket approval applications and approvals indicate that there is no consistent trend in either measure over the last seven years of the program. Applications range between 60 and 97 per year; approvals range between 24 and 72; a total of 323 applications were approved between 1976 and 1986. In addition, FDA received almost 2,400 "premarket approval application supplements" between 1980 and 1986; roughly 1,900 of these were approved. The number of supplements has been increasing in recent years. These supplements represent modifications to the design, manufacture, or labeling of a device with an approved premarket approval application. While usually not subjected to the same level of scrutiny (for example, panel review) as original applications, supplements are still reviewed to provide reasonable assurance that the modification will not adversely affect the safety and effectiveness of the device.

Recent years have seen a marked decrease in the backlog of applications to be considered (72 applications were approved in fiscal year 1986), and a decrease in the length of time it takes to review applications should result. FDA announced in late 1987 that the review backlog had been eliminated. Ophthalmic devices, and transitional devices in general, accounted for the largest proportion of both applications and approvals. Pacemakers, heart valves, and transcutaneous carbon dioxide monitors are among the non-transitional devices to receive approval. FDA has also approved new "breakthrough" technologies such as magnetic resonance imagers, the extracorporeal shockwave lithotripter, single and multichannel cochlear implants, variable rate pacemakers, and implantable cardiac defibrillators.

Implementation of premarket approval for preamendment devices (and substantially equivalent postamendment devices) has been considerably slower. Roughly 150 types of preamendment devices have been placed (or proposed for placement) in class III. Through the end of 1986, almost 2,000 premarket notifications for postamendment devices had been found substantially equivalent to these preamendment devices. Processing premarket approval applications for all of these devices will obviously be a major undertaking. Using FDA estimates of 1,200 staff hours to process a premarket approval application and 1,700 hours per staff year, it would take 11 years for the current staff (that is, almost 1,400 staff years) to process applications for just the 2,000 devices found substantially equivalent to preamendment class III devices—without considering either the ongoing work load or the preamendment class III devices.

The first final regulation requiring premarket approval for preamendment devices (and substantially equivalent postamendment devices) was published in June 1984. Since then, the process has been initiated for eight additional types of devices. No applications were received for either intrauterine devices (IUDs) or the implanted cerebellar stimulator. One application for a diaphragmatic and phrenic nerve stimulator was received and eventually approved.

As of the end of fiscal year 1987, reclassification petitions had been filed for the automated differential cell counter and the infant radiant warmer and were being considered. Premarket approval applications for preamendment (and substantially equivalent postamendment) heart valves were due in December 1987; 8 to 10 applications were

expected—fewer than half of the number originally estimated to be submitted. Final rules requiring applications for contraceptive tubal occlusion devices and transabdominal amnioscopes (fetoscopes) had been published; applications were to be filed by early 1988.[12]

Early reactions of the device industry to the call for applications for premarket approval for preamendment (and substantially equivalent postamendment) devices suggest that it will be difficult to judge the resources required to fully implement this provision. On the one hand, no applications were generated for some of the devices. On the other hand, if reclassification actions are filed for many of the class III devices, resources will be required to process those actions, in addition to the resources to process the applications for premarket approval should reclassification be refused. Any proposal to speed this process would have to consider these resource issues.

Summary and Implications

FDA has been reviewing premarket approval applications since soon after the amendments were enacted. Much of the premarket approval workload involves transitional devices, and particularly ophthalmic devices. Until late in 1986, the reviews were conducted under guidance contained in regulations proposed in 1980 but never made final. Those regulations were made final in 1986, with several significant changes in policy.

FDA has been slow to bring preamendment (and substantially equivalent postamendment) devices under premarket approval. The amendments specify a minimum grace period of 30 months that FDA must wait prior to beginning the process for any particular type of device. At the time this report was written, only nine device types had been required to undergo premarket approval. More than five years have passed since the expiration of the grace period for three categories of devices: neurology, cardiovascular, and obstetrics and gynecology. While the statute does not establish a maximum time within which the process must be accomplished, it is our opinion that FDA's progress is not adequate. However, we accept FDA's argument that resources have been limited and priorities have had to be set.[13]

[12]At the time the report was reviewed, FDA was preparing a list of 20 to 30 additional "high priority" class III preamendment devices as candidates for premarket approval. At that time, they planned to publish the list within a few months.

[13]Information on the Office of Device Evaluation's fiscal year 1985 and 1986 workload and resources is presented in chapter 4. (See pages 56 to 58.)

The Relationship of Premarket Notification to Postmarketing Compliance Activities

Once a device is placed into commercial distribution through one of the premarketing review mechanisms, it becomes subject to a variety of additional provisions of the act also administered by FDA. The firm must be registered and its devices listed with the Office of Compliance. The listing triggers a schedule of inspections for compliance with Good Manufacturing Practices and other provisions of the act. In addition, the Office of Compliance is responsible for making determinations concerning whether a particular product is a device and whether a product's labeling is appropriate.

In each of these areas, the premarket notification program must coordinate with the respective compliance programs. In exploring with FDA officials the implications of our finding that as many as 20 percent of premarket notifications were not placed in one of the three classes, we discovered that no systematic mechanism exists within FDA for linking premarketing review with postmarketing programs for ensuring compliance. That is, although premarketing review, in theory, is closely related to postmarketing review, in practice it is difficult for FDA to connect one to the other.

For example, ODE's information on the determinations of substantial equivalence and the subsequent placement of devices in appropriate regulatory classes through premarket notification is incomplete. Only recently has the information become available in an automated form so that it could be used easily in postmarketing compliance programs. In addition, when a manufacturer files a new listing, the Office of Compliance does not routinely review premarket notification decisions to check whether the manufacturer has filed a premarket notification or if the manufacturer has reported the same product code as assigned in premarket notification.

Similarly, information obtained by the Office of Compliance through registration and listing of medical devices by manufacturers as well as through device reporting (that is, the Device Experience Network) is difficult for premarket notification reviewers to access. As a result, it is difficult for reviewers to use this information to determine whether any of the devices they are reviewing are associated with reports of problems.

Finally, restrictions placed on the marketing of individual products during premarket notification made by telephone and not included in the decision letter, and reports to ODE staff of noncompliance with labeling and other requirements, are not systematically reported to the Office of

Compliance. Procedures for follow-up by this office are also not systematic.

Summary and Conclusions

While the pace of implementing the amendments slowed notably after the first few years, initial classification of preamendment devices is, or soon will be, completed with the publication of classification regulations for radiology and general and plastic surgery devices. The reclassification of some class II devices into class I and the exemption of up to 50 percent of class I devices from premarket notification appear to be the next steps. These steps could reduce the number of premarket notifications that occur in the future. While used relatively infrequently, reclassification is a procedure for dealing with devices found not substantially equivalent that may become more important as FDA reconsiders its reclassification policy. The premarket approval process for transitional devices and those found not substantially equivalent to predicate devices has been implemented and appears to have overcome early problems concerning the timeliness of reviews.

Implementing regulations for the premarket notification process were published as required by the statute. Those regulations clearly stated FDA's intent to make determinations of substantial equivalence as part of the premarket notification process. FDA's position on determinations of substantial equivalence was clarified and strengthened in June 1986 by the issuance of a memorandum to ODE reviewers detailing how determinations should be made and providing illustrative examples. However, the fact that most postamendment devices and device modifications are marketed through premarket notification, rather than premarket approval, has raised concern about the relative role of these review processes in regulating medical devices. We explore FDA's policies and the actual operation of the premarket notification program in much greater detail in the following chapters.

Finally, our finding that a relatively large percentage of premarket notifications were not assigned to a particular class led to the discovery that the linkage between the Office of Device Evaluation, the office responsible for premarketing reviews, and the Office of Compliance, the office responsible for postmarketing activities, is weak and not systematic. Each office has information that could be quite useful to the other in carrying out its responsibilities. The problem is more than a simple coordination issue; improvements need to be made in regard to the availability of information between these offices and in its comparability.

The lack of formal performance standards for class II devices and the relatively slow implementation of the premarket approval review of preamendment (and substantially equivalent postamendment) class III devices are two exceptions to this generally positive situation. In the case of preamendment (and substantially equivalent postamendment) class III devices, FDA has shown that it is now ready to move forward with premarket approval applications on high priority devices. Whether the pace is rapid enough is a matter of judgment and priorities. However, it should be noted that until the premarket approval process is completed, postamendment class III devices may continue to be reviewed and marketed through premarket notification. Similarly, the lack of performance standards means that no formal distinction can be made in premarket notification between a class I device and a class II device.

Matter for Congressional Consideration

FDA has failed to implement significant portions of the regulatory scheme enacted in the Medical Device Amendments of 1976--most notably, performance standards and premarket approval for preamendment devices. These failures have resulted in premarket notification carrying a greater regulatory burden than it would if the system had been fully implemented. In part, the implementation failures are the result of a shortage of resources and the focusing of FDA priorities on other program activities, including review of premarket notifications and premarket approval applications for transitional and not-substantially-equivalent devices.

The additional resources that would be required to fully implement the amendments as enacted are difficult to estimate but would be great. Further, the need for performance standards for all class II devices has been questioned. In the absence of the resources necessary to fully implement the amendments, we believe FDA should have the flexibility to tailor the level of performance review required to the risks of the device and available staff resources. For class II devices, some options for accomplishing this latter goal include incorporating voluntary standards into formal performance standards, simplifying the administrative procedure, or reclassifying low-risk class II devices into class I. For preamendment class III devices, making the panel review of premarket approval applications optional—thus allowing FDA to determine what data are required—and making more use of supplements, are options that could be considered.

In light of these issues, the Congress may want to consider (1) clarifying the extent to which FDA should evaluate, within the premarket notification process, the effects of technological changes in medical devices on their safety and effectiveness (see page 21) and (2) developing alternative approaches to the regulation of devices currently placed in classes II and III that could accomplish the original purposes of the amendments (see pages 33 to 39).

Implementation of Premarket Notification: Policies for Determining Substantial Equivalence

Within the broader context of medical device premarketing review presented in the previous chapter, the primary focus of this chapter is on specific FDA policies for determinations of substantial equivalence. We describe FDA's informal guidance to manufacturers during the early years of the program, examine internal changes brought about by the reorganization of the FDA units responsible for medical devices, and evaluate the formal guidance memorandum developed by the Office of Device Evaluation in 1986 for reviewers to follow in determining substantial equivalence. Finally, we emphasize that a determination of substantial equivalence is, ultimately, a professional and scientific judgment that must be made on a case-by-case basis. That judgment can be guided by policies but never completely determined by them.

Guidance to Manufacturers on Determinations of Substantial Equivalence

Until June 1986, FDA had not developed any formal written guidance for making determinations of substantial equivalence for reviewers to follow. However, over the years, FDA has published a variety of materials designed to provide guidance for the device industry on FDA expectations. In particular, FDA published an extensive workshop manual in 1983 that details the various regulatory requirements that manufacturers of medical devices must meet, including those for premarket notification.[1]

With respect to premarket notification, the manual contains the preamble to the final regulation, the regulation itself, a journal article describing premarket notification, information on exemptions from premarket notification, and four sample notifications. It also contains a description of what FDA expects from manufacturers who submit notifications, and what FDA does when a notification is received.

While the regulation itself does not indicate the basis upon which a determination of substantial equivalence will be made, the workshop materials do provide some information in this regard. In describing how the reviewers go about making a decision, the manual indicates that the first step is deciding whether the "new" device (that is, the one being considered for marketing) falls within one of the roughly 1,700 types of devices contained in two broad categories. The first category consists of devices that were on the market prior to the amendments; the second, of devices reclassified into class I or class II since the amendments were

[1]U.S. Department of Health and Human Services, Food and Drug Administration, Regulatory Requirements for Medical Devices: A Workshop Manual, FDA 85-4165 (Washington, D.C.: U.S. Government Printing Office, 1985).

enacted.[2] Next, the reviewer determines whether the new device performs the same function as a predicate device. Finally, the reviewer considers any differences between the new device and the predicate device and the potential effect of these differences on safety and effectiveness. If the differences are not material to safety and effectiveness, the new device is found substantially equivalent. If the differences are material to safety and effectiveness, additional data may be required to demonstrate substantial equivalence.

Concerning judgments about whether differences are material to safety and effectiveness, the workshop manual advises manufacturers that reviewers may request any kind of testing data, including clinical data, deemed necessary to demonstrate that the new device will perform at least as well as the predicate device. The amount of data that may be required varies depending on the types of questions that need to be answered and the complexity of the device. While FDA does not require the manufacturer to have manufactured the device prior to filing a notification, a request for testing information would force the manufacturer to produce at least a prototype of the device in order to generate the required data.

The manual is clear in pointing out that premarket notification does not determine whether a device is safe and effective. The process of premarket notification is designed to examine the performance of a new device relative to that of a similar predicate device. However, FDA does argue that this examination of relative performance allows them to keep off the market devices that present unanswered questions of safety and effectiveness relative to comparable predicate devices, that appear less safe or effective than predicate devices, or that have intended uses or technology sufficiently different to prevent adequate comparisons with predicate devices. (Because our study was not designed to address outcomes of premarket notification, we cannot assess the validity of these claims.)

The presentation in the workshop manual regarding determinations of substantial equivalence is consistent with the less restrictive reading of the guidance in the house report. It provides for a consideration of intended use, technological differences between the "new" device and the predicate device, and the potential effects on safety and effectiveness of the technological changes. FDA puts manufacturers on notice, as

[2]A device that falls into either of these two categories is termed a "predicate device."

it did in the implementing regulation, that it will ask for whatever information it deems necessary to make an assessment of substantial equivalence. The emphasis on performance could even be interpreted as a precursor to review of compliance with performance standards.

The Premarket Notification Criticism Task Force

FDA initiated many activities in response to early criticisms of the implementation of the amendments. In October 1982, FDA combined the Bureau of Medical Devices and the Bureau of Radiological Health into the Center for Devices and Radiological Health. In early 1984, eleven internal task forces were established to examine a wide range of topics related to implementation of the amendments, including premarket notification, and to recommend changes as needed.

The task force on premarket notification, known as the Premarket Notification Criticism Task Force, examined three broad questions based on criticisms of FDA's implementation of premarket notification.

- When should a 510(k) submission be made, and how should FDA ensure compliance with 510(k) requirements?
- How can 510(k) submissions be expeditiously but adequately processed?
- What is the meaning of substantial equivalence, and what data are necessary to reach a decision?

The task force made a number of recommendations to the management of the Center for Devices and Radiological Health. (See appendix IV for a list of the recommendations.) Some of the recommendations have already been implemented, including improved information systems, decentralization of decision making, creation of "expedited review procedures" for class I devices, and formal guidance on how determinations of substantial equivalence should be made. Additional changes, including improved documentation and more extensive reviewer training, are planned.

We believe that the changes have streamlined the decision-making process and formalized policies that were in place earlier. The changes are sensible responses to the criticisms and have already resulted in decreases in review time and more efficient handling of the large volume of premarket notifications. Furthermore, planned changes in documentation and reviewer training should result in an improved data base that makes monitoring of the premarket notification program easier for both FDA and external evaluators.

Current FDA Guidance on Determinations of Substantial Equivalence

In examining how reviewers made decisions about substantial equivalence, the task force concluded that, while some variations in interpretation existed within ODE, past practices were generally acceptable. However, the task force also determined that the informal rules applied by reviewers should be clarified in a written guidance that contained scientifically and legally defensible criteria for making determinations of substantial equivalence. That guidance was developed and issued in a memorandum dated June 30, 1986, from the director of ODE to ODE reviewers.

Figure 3.1, reproduced from that document, is a detailed flowchart that lays out the questions FDA reviewers must answer in making determinations of substantial equivalence. In addition, the memorandum documents the history of premarket notification, defines key concepts, and provides examples of situations in which a device would or would not be found equivalent.

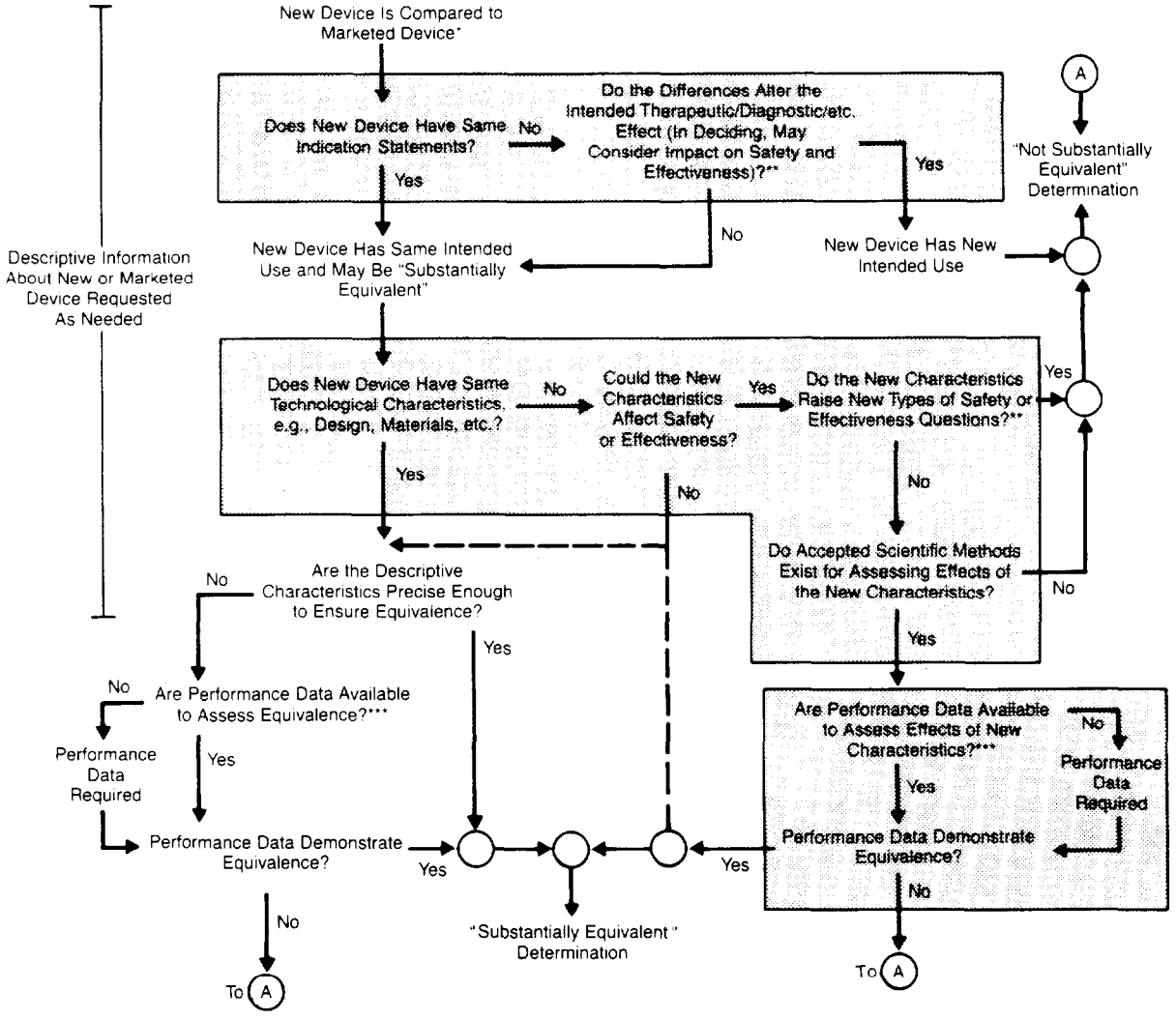
The guidance in the memorandum appropriately addresses the primary parameters pertaining to intended use, technological characteristics, and the safety and effectiveness of the device under review and is consistent with the less restrictive reading of the house report. We would like to emphasize again that day-to-day decisions on individual notifications must still depend on the professional judgment of the reviewers. In addition, several potential areas of concern were identified.

Intended Use

How similar the intended use of the new device must be to that of the predicate device depends on the type of device under review. (See the top shaded box in figure 3.1.) For some types of devices, typically diagnostic in function, the interpretation of "same intended use" is very broad. For example, a test to diagnose legionnaire's disease has been marketed under premarket notification, although no such tests existed prior to 1976. In fact, the disease had not been identified prior to 1976. There were, however, tests for other respiratory diseases. In addition, a device to detect changes in the lens of the eye based on the pattern of reflected light was found substantially equivalent to a device used to diagnose unrelated diseases of the eye through observation of the interior of the eye.

For certain other devices that are primarily treatment-oriented, a change in body system or method of administration may be sufficient to invoke extensive review and sometimes rejection. For example, lasers

Figure 3.1: Flowchart Representing Determination of Substantial Equivalence



*510(k) Submissions Compare New Devices to Marketed Devices. FDA Requests Additional Information if the Relationship Between Marketed and "Predicate" (Pre-Amendments or Reclassified Post-Amendments) Devices Is Unclear.

**This Decision is Normally Based on Descriptive Information Alone. But limited Testing Information is Sometimes Required.

***Data May Be in the 510(k), Other 510(k)s, The Center's Classification Files or the Literature.

Source: FDA/ODE memo on determinations of substantial equivalence. (Boxes added to aid presentation.)

were accepted within the medical community and used for certain procedures prior to 1976. The same lasers used for other procedures, or different lasers used for those same procedures, have been required to have additional performance data or have been found not substantially equivalent.

We believe this policy of permitting variation in the definition of "intended use" is consonant with the admonition in the house report that substantial equivalence be broadly interpreted in situations where safety and effectiveness are not at issue and more narrowly when safety and effectiveness may be affected. Diagnostic devices, particularly those used in noninvasive procedures, typically present little risk to the patient as long as they are at least as accurate as the comparison device. Conversely, a minor change in the intended use of a treatment device could represent important new risks for the patient.

Effects of Technological Changes

Changes That Do Not Affect Safety and Effectiveness

The guidance developed by ODE contains a set of questions for evaluating the effects on safety and effectiveness of changes in the technological characteristics of a device. (See the middle shaded box in figure 3.1.) If the changes would not affect safety and effectiveness, the guidance indicates that there is no need to continue on to additional questions, and the device is determined to be substantially equivalent. However, we believe that an examination of performance is still warranted before a determination of substantial equivalence is made. (See the dashed arrow below the middle shaded box in figure 3.1.) When we discussed this with an ODE official, he indicated that a comparison of performance would be done routinely, and that therefore making this change would not affect the actual operation of the program. In general, we agree with this position.

New Types of Safety and Effectiveness Questions

The next question in the flowchart concerns whether the types of questions posed by the change in technological characteristics are different from those that would be raised about the predicate device. According to the guidance, if the types of questions concerning safety and effectiveness are different from those for the predicate device, a not-substantially-equivalent determination should automatically be made. This

approach is consistent with the less restrictive reading of the house report.

However, in the course of our review of premarket notification files, we observed several cases in which the reviewer's notes indicated that differences in the device posed new questions of safety and effectiveness, but nevertheless the final decision was not "not-substantially-equivalent." While we cannot answer the question of whether the device did, in fact, present "new types" of questions, we feel that reviewers should be more thoroughly trained in following the guidance, and that management should pay closer attention to the guidance and the documentation of decisions when they review the reviewer's recommendations.

Accepted Scientific Methods

The final question in this part of the flowchart asks whether an accepted scientific method exists for assessing the effects of the new characteristics in regard to the identified safety and effectiveness questions. If not, the device should be found not-substantially-equivalent. Read literally, this question would be rendered moot by FDA's determination that clinical data are acceptable in a premarket notification. That is, "an accepted scientific method," such as the clinical trial, usually exists and could be requested. If this were true, this portion of the guidance could be greatly simplified.

However, in discussing this point with an FDA official, we discovered that our interpretation of this part of the guidance is quite different from FDA's. Rather than focusing on acceptable methods as we did, FDA focuses on whether there is scientific agreement about what the important issues of safety and effectiveness are for the device in question, and whether an adequate comparison in terms of relative safety and effectiveness can be developed. That is, what are the important outcomes to measure and can data on those outcomes be developed? Interpreted in this manner, the question is no longer moot and is, in fact, reasonable and important. We feel that the guidance in this area, including the flowchart, should be revised to more accurately and clearly reflect this emphasis.

Performance Data

Critics of FDA's implementation of premarket notification have suggested that FDA exceeded its authority in terms of both the type and extent of performance data required to support claims of substantial equivalence. (See the bottom shaded box in figure 3.1.) Few people would contest the notion that some level of performance review is appropriate within

premarket notification and, therefore, so is the requirement for some type of performance data. However, the criticism voiced by some is that FDA is requiring too much performance information, particularly clinical data. Indeed, the criticism that FDA is doing "mini-PMAs" (mini-premarket approvals) in premarket notifications is directly linked to its requirements for performance-testing data.[3]

FDA argues that clinical data in a premarket notification answer questions concerning the comparable safety and effectiveness of the device under review and a predicate device. Similar data in a premarket approval application pertain more directly to the risks and benefits of the particular device under review. This policy is firmly established in practice, and the industry is probably willing to continue to accept this practice because of the implications of the alternative—premarket approval. On the other hand, FDA noted in the final report of the Premarket Notification Criticism Task Force that requests for data in a premarket notification sometimes may be directed more at PMA-type issues of safety and effectiveness than at comparative issues.

We believe that FDA's policy on the use of clinical data in premarket notification is sound and, if implemented as set out in the guidance memo, would be consistent with assuring that "new" devices are substantially equivalent to predicate devices in terms of performance. We found no evidence on how well FDA implements this policy and, given the relative lack of documentation in premarket notification files, believe that there is virtually no way to obtain it—short of replicating the review process. We do present data in the next chapter on the type and extent of testing information that is contained in premarket notification files.

Comparison to a Predicate Device

As discussed in chapter 2, the statute requires that substantial equivalence determinations be made relative to specific predicate devices. Predicate devices are either devices that were in commercial distribution prior to the amendments or postamendment devices that have been reclassified into class I or class II. While some change in technology is appropriate under the definition of substantial equivalence, stringent reliance on pre-1976 technology as a reference point would, over time, have the effect of "freezing" technology.

[3]The changes sought by critics depend on whose interests they represent. Broadly speaking, those who represent the medical device industry suggest that FDA does not really need all of the performance data they are requesting in order to make determinations of substantial equivalence. Those who represent consumer-oriented interests suggest that FDA is making decisions in premarket notification that should more appropriately be made in the premarket approval process.

As Figure 3.1 indicates, FDA policy mirrors the statutory requirement by also limiting its reviewers to making comparisons to predicate devices. In submitting notifications, manufacturers are permitted by FDA to make their comparisons to other devices marketed through premarket notification, rather than to specific predicate devices. FDA initially assumes the responsibility for identifying an appropriate predicate device. If that proves difficult, the manufacturer is ultimately responsible for providing the necessary information on a predicate device.

While the statute does provide the alternative of using reclassification to establish a new "standard" of comparison, this approach has proven administratively burdensome and resource intensive and is seldom used. (See chapter 2.) To date, FDA has not felt so constrained by the preamendment device requirement that it has adopted the strategy of using reclassification. As shown in chapter 2, the percent of premarket notifications found not substantially equivalent has not increased, and very few reclassification petitions have been filed. Nevertheless, the potential for constraining the introduction of new medical technology remains.

Proposals have been made to change the referent for substantial equivalence determinations from predicate devices to "currently marketed" devices. We believe that this change would be useful. At present, if manufacturers can demonstrate that their devices are used for the same purposes and perform as well as products marketed prior to 1976, FDA must find the products substantially equivalent even if there are other products already on the market that "work better." If the referent were changed, FDA could presumably find such devices not substantially equivalent based on their lower performance than currently marketed products, even in the absence of performance standards.

Summary and Conclusion

We conclude that FDA's implementing regulations and policies for determining substantial equivalence are consistent with the less restrictive reading of the guidance provided in the house report. The implementing regulation on premarket notification indicated that determinations of substantial equivalence would be actively made as part of the premarket notification process. While the exact content of a premarket notification was not fully specified, FDA did place the industry on notice that it would request whatever additional information it deemed necessary to make a determination of substantial equivalence. It also made clear that devices should not be marketed before a determination was made. Informal guidance to manufacturers in the form of workshop

materials and other resources was developed and made available to the industry; more formal guidance was developed later.

We have made a number of observations about the formal guidance, its interpretation, and the need for clarification. For example, when changes in the technology of a device do not affect safety and effectiveness, reviewers should still consider performance issues prior to finding the device substantially equivalent. Additional reviewer training and supervision is needed to assure that when new types of questions regarding safety and effectiveness are raised, the device is found not substantially equivalent. Finally, the guidance with respect to "accepted scientific methods" requires clarification. If the intent is to determine whether enough is known about the device to specify relevant questions about safety and effectiveness and to gather adequate comparison data, the guidance should be revised accordingly.

There is one point that we believe requires congressional attention at this time. The standard of comparison for determinations of substantial equivalence should be "currently marketed" devices rather than predicate devices, because FDA's interpretation of the statute has had the effect of "freezing" technology at 1976 levels.

Recommendation

GAO recommends that the Congress amend the Federal Food, Drug and Cosmetic Act to make the determination of substantial equivalence relative to a currently marketed device rather than a predicate device. This can be accomplished by amending section 513(f)(1)(A)(ii) of the act (21 U.S.C. 360(c)(f)(1)(A)(ii)) to read as follows:

"is substantially equivalent to a currently marketed device within such type, regardless of when that currently marketed device was introduced or delivered for introduction into interstate commerce, or ...."

While some technological change has been accommodated within the current statute, it is clear that such accommodations would eventually become impossible. The proposed change would eliminate this problem and give FDA clear authority to permit changes in device technology that fall within the definition of substantial equivalence.

Agency Comments

HHS provided official comments on an initial draft of this report, characterizing the report as thorough and fair and concurring with GAO's recommendations to the secretary of HHS. (See appendix VI.) The initial

draft portrayed FDA's regulations and policies as generally consistent with the statute and legislative history. GAO subsequently decided that the legal status of the regulations and policies was not germane to the thrust of the report and therefore made appropriate revisions. The revisions do retain the observation that the regulations and policies adopted by FDA are consistent with a less restrictive reading of the house report. FDA found the revised draft to be less satisfactory than the original, expressing concern that the revisions contained inaccurate or inappropriate statements. In particular, FDA stated that the revised draft compares FDA's program with a restrictive reading of the statute that is neither consistent with the legislative history nor practical to implement.

We disagree with FDA's views on our revised report for two reasons. First, we are not comparing FDA's program to the restrictive reading. We are positing two alternative readings and noting that FDA's program is generally consistent with the less restrictive reading. Second, we do not imply that FDA should, or could with its present resources, operate according to the more restrictive reading.

The Implementation of Premarket Notification: Day-To-Day Operation

In this chapter, we examine the day-to-day operation of the premarket notification program to determine how its regulations and policies are actually implemented in day-to-day decision making. We present an overview of program administration and operations and then consider three indicators of their adequacy.

- Is there documentation of how FDA makes determinations of substantial equivalence for individual devices?
- Are premarket notifications reviewed by individuals with enough scientific knowledge and background to make reasonable decisions about substantial equivalence?
- Is FDA's guidance for making determinations of substantial equivalence applied consistently to similar devices?

Finally, we evaluate two specific issues that the committee asked us to consider that are related to our objective of determining whether FDA operates the premarket notification program appropriately.

- Is FDA finding too many devices substantially equivalent?
- Is FDA conducting "mini-PMAs"?

Administrative Structure for Processing Premarket Notifications

It is important to understand the administrative structure and routine review activities involved in premarket notification as a framework for considering the adequacy of FDA's daily operation of the premarket notification program. These components of the premarket notification program are described below.

Organizational Structure

While the implementation of the premarket notification provision is evolving and becoming increasingly formalized, the basic organizational structure of the review process has not changed for some time. The Center for Devices and Radiological Health, created by the merger of the Bureau of Medical Devices and the Bureau of Radiological Health in 1982, is one of the five centers of the Food and Drug Administration (FDA), Public Health Service, Department of Health and Human Services. It has the overall responsibility for implementing the act in the area of medical devices. Within The Center for Device and Radiological Health, the Office of Device Evaluation (ODE) develops and implements national programs to protect the public health by assuring the safety, effectiveness, and proper labeling of medical devices through premarketing review (including premarket notification and premarket approval).

Overall management responsibility for ODE resides in the office of the director, which consists of the director, a deputy director, and an associate director. However, management of the day-to-day activities of the premarket notification program is decentralized. The 510(k) coordinator, who is administratively separate from the review process, is responsible for processing the paperwork for premarket notification and for liaison with other offices within The Center for Device and Radiological Health. The actual review of premarket notifications by FDA occurs within one of seven divisions organized by medical specialty or organ system. Each division is headed by a director and deputy director. The divisions are further subdivided into branches that review particular types of devices. Branches are headed by branch chiefs who both supervise the individuals who conduct the scientific reviews and provide reviews and assistance in their area of expertise.

The bulk of the Office of Device Evaluation's workload involves the review of premarket notifications, premarket approval applications, and investigational device exemption requests. (See table 4.1 on page 57.) As the table shows, the number of individual applications that must be processed in any given year is substantial. In 1986, a total of slightly over 13,000 applications were received. In addition to its three primary responsibilities, the Office of Device Evaluation also handles the classification of preamendment devices, reclassification petitions, and premarket approval applications for preamendment devices.

Table 4.1: ODE Review Workload for Fiscal Year 1985 and Fiscal Year 1986

Type of submission	FY 1985	FY 1986
Premarket notification		
Original notifications	5,254	5,063
Supplements	1,800	2,050
Subtotal	**7,054**	**7,113**
Investigational device exemptions		
Pre-original applications	21	20
Original applications	204	206
Amendments	366	275
Supplements	2,457	2,884
Subtotal	**3,048**	**3,385**
Premarket approval		
Original applications	97	69
Amendments	597	853
Supplements	393	478
Amendments to supplements	628	714
Reports for original applications	236	297
Reports for supplements	132	174
Subtotal	**2,083**	**2,585**
Total	**12,185**	**13,083**

Source: FDA/ODE fiscal year 1986 annual report

The Office of Device Evaluation staff totaled 176 "full-time equivalents" (FTEs) in fiscal year 1985 and 179 FTEs (plus 8 FTEs on detail from other FDA offices) in fiscal year 1986; the fiscal year 1987 allocation was 190 FTEs. These numbers include all professional, administrative, clerical, and supervisory staff. In fiscal year 1985, there were 119 professional and administrative staff who were involved in the technical aspects of reviewing applications and making final decisions. This means that there were slightly more than 100 submissions per technical reviewer in fiscal year 1985.

In fiscal year 1985, the Office of Device Evaluation estimated that it had had an FTE shortfall every year since fiscal year 1983 of approximately 16 FTEs, which accounted for the lengthy review periods and backlog of applications. The increase of 14 FTEs in fiscal year 1987 is one of the reasons cited by the Office of Device Evaluation for the elimination of the backlog of applications and the decrease in review time. New policies, implemented in 1986, delegating signature authority on premarket notifications to the division directors and allowing branch chiefs to

decide when premarket notifications for class I devices need only minimal reviews are also partially responsible for improvements in processing time for submissions. Early in fiscal year 1988, FDA announced that the backlog of applications had been eliminated.

Document Control and Coordination

When a manufacturer submits a premarket notification to FDA, it is routed to the Document Mail Center and logged in by the staff of the 510(k) coordinator.[1] The date and time of arrival, the manufacturer's name and address, and the reviewing division are entered into a computerized data base, and the submission is assigned an unique document number. The submission is then directed to the appropriate division.

Concurrently, the manufacturer is sent a letter acknowledging receipt of the submission. The letter advises the manufacturer to wait at least ninety days from the date of FDA receipt, or until FDA has found the device substantially equivalent, before placing the product into commercial distribution. The manufacturer is also informed of the FDA-assigned document number and asked to refer to it in all subsequent communications regarding the submission. Copies of this letter and all other correspondence between manufacturers and FDA were contained in the submissions we reviewed.

If additional information is required and has been requested from the manufacturer during the review process, reviewers are encouraged to return the notification file to the Document Control Center as a matter of policy. When the file is returned to the Document Control Center, the manufacturer is sent a letter informing him that the notification is being held pending receipt of the requested information. The manufacturer is also informed that another ninety-day period will begin once the requested information is received and that the notification will be considered withdrawn unless he responds within thirty days. If the reviewer does not return the file to the Document Control Center, the ninety-day "clock" continues to count down.

After the reviewer's preliminary decision has been reviewed by the branch chief and the division director, the file is returned to the Document Control Center for the preparation of a "decision letter" appropriate to the final determination. The decision letter is FDA's formal

[1]Although most premarket notifications are submitted by manufacturers, other parties (such as repackagers and distributors) also submit premarket notifications. We will use the term "manufacturer" generically to mean the submitter of a premarket notification.

notification to the manufacturer of the decision on substantial equivalence. Standard letters have been developed for most decisions (for example, substantially equivalent or not substantially equivalent), although the letter can be tailored to the individual situation as required. Nonstandard letters, as well as some standard letters, require the manufacturer to comply with certain restrictions prior to marketing. These cases are referred by the 510(k) coordinator to the Office of Compliance for review. Once all of the reviews are completed, the decision letter is signed and sent to the manufacturer.[2]

How Premarket Notifications Are Reviewed

The day-to-day review of premarket notifications is managed by the branch chiefs within ODE and conducted by scientific reviewers. The branch chiefs are responsible for making initial judgments about the intensity of review required, for assigning the notifications to reviewers, and for reviewing the preliminary decisions for soundness and adherence to ODE policy. The reviewers conduct the in-depth reviews and develop a preliminary judgment about substantial equivalence.

Prereview by Branch Chiefs

Submissions are routed from the Document Mail Center to the appropriate branch chief within each of the divisions. The branch chief verifies that the submission has been correctly routed and quickly assesses the level of review that will be required. As a matter of formal ODE policy, which is described in guidelines issued to reviewers (known as the "Blue Book"), all divisions should sort notifications for class I devices into one of four categories based on the types of questions that need to be addressed in the review.[3] Notifications involving devices in class II or class III should receive full review. In interviews with branch chiefs and reviewers, we found that none of the divisions had followed this process as described by the guidelines. Branch chiefs in each division did indicate that they tell reviewers to give certain notifications more scrutiny than others; they also identify specific problems or issues that the reviewer should examine and evaluate. (Neither the formal nor informal "sorting" of notifications was routinely documented in the files we examined.)

[2]Standard decision letters are signed by the division directors; nonstandard letters are signed by ODE management.

[3]Within Class I, a device exempt from the premarket notification requirements is designated a category I device. A device proposed for exemption or one that does not raise any question concerning substantial equivalency is category II. A device that raises only minor questions concerning substantial equivalency of the sort that can be easily resolved is category III. A device that raises questions of substantial equivalency that require scientific review or verification of data is category IV.

After making this initial assessment, the branch chief assigns the submission to a reviewer or team of reviewers with one lead reviewer. The primary basis of the assignment is the expertise or familiarity of the reviewer with the device under review. The workload within the branch and the experience of the reviewer are also considered in the assignment. In only one division—the Division of Obstetrics and Gynecology, Ear, Nose, Throat, and Dental Devices—was explicit mention made of reviewers being encouraged to review submissions as teams. Nonetheless, in all divisions, some submissions were reviewed by more than one reviewer because of the special expertise or experience that the additional reviewer(s) could bring to the review. Our interviews with FDA officials indicated that the branch chief also functions as a source of scientific assistance, including providing suggestions about where to seek additional help and making the reviewers aware of any relevant policy issues.

Review of Premarket Notifications

The fundamental decision made in the review of a premarket notification is whether a device is substantially equivalent to a predicate device. Although the reviewer's recommendation is circumscribed by ODE policy and reviewed by ODE management, the reviewer's scientific judgment is the primary mechanism through which a determination of substantial equivalence is made. Voluntary standards and guidance about a particular device, when they exist, are also used by the reviewers in arriving at a determination.

In addition to other reviewers and ODE policy and management, the resource most commonly used by reviewers is earlier premarket notifications for similar devices. On occasion, the reviewer may also consult files maintained by the Office of Compliance (for example, registration, listing, and postmarketing surveillance files) in The Center for Device and Radiological Health. These files allow reviewers to examine the reviews of similar device types and to determine what questions, if any, may have been raised by the Office of Compliance about a particular type of device.

Although we did not find them documented very often in the submissions we reviewed, FDA officials indicated that a reviewer can also take advantage of a number of sources of assistance outside ODE. These sources include other FDA offices (such as the Office of Science and Technology within the Center for Device and Radiological Health), the Public Health Service (for example, the Centers for Disease Control, National Library of Medicine, and the National Institutes of Health), other federal

agencies (for example, the National Bureau of Standards, National Aeronautical and Space Administration, and the military laboratories), and the experts who make up the premarket approval and classification panels. On some occasions, experts from academia may also be called upon for assistance.

Based on our review of submissions, we found that the amount of information submitted to FDA for review in the original premarket notifications varied substantially. (See table 4.2.)[4] Some submissions have little more than the statutorily required material (that is, the device classification and description, and a statement of actions taken to comply with the performance standard and premarket approval provisions of the amendments). Other applications have many pages of comparisons with other devices, journal literature on that type of device and its use in clinical practice, performance data, and other documentation. In addition to the manufacturer's registration number and proposed classification, the most frequently submitted materials are the package labels and operating instructions or package insert for the subject device. A sample of the device is generally not submitted, nor is it required by FDA.

[4]The information on the contents of premarket notification files presented in the following tables represents weighted estimates based on our sample of cases. As such, the estimates of both percentages and numbers of submissions are subject to sampling error of no more than ± 6 percent with an 85 percent confidence interval. (See appendix II.)

Table 4.2: Contents of 1986 Original Submissions for "New" and Comparison Devices[a]

Submission contents	"New" device[b]	Comparison device[b]
General information		
Registration number[c]	82%	[d]
Class from manufacturer	72	[d]
Sample device	3	[d]
Advertising	33	29%
Operating instructions	65	21
Package labeling	67	10
Picture or drawing	49	22
References or articles[c]	33	[d]
Other material[c]	33	[d]
Testing information		
Diagnostic devices	44	[d]
Treatment devices[e]		
Bench test	20	[d]
Animal test	3	[d]
Test protocol	0	[d]
Human test	4	[d]

[a]The total number of original submissions in 1986 was 5,111. Of those, 4,726 submissions were included in our universe. (See appendix II.)

[b]The "new" device is the subject of the notification; the comparison device is the device to which equivalence is claimed.

[c]Refers to information in the submission that does not necessarily pertain directly to the device under review.

[d]Not applicable

[e]The category of treatment devices includes all devices that are not primarily diagnostic in function.

The types of additional or supplemental information requested of the manufacturer and the questions asked by FDA are determined by several factors. Across all submissions, information concerning the device's components, design, and testing was requested most frequently. (See table 4.3 on page 63.) The types of questions also varied depending on the type of device. Questions about testing and requests to change the labeling were the most frequent types of request for diagnostic devices, while questions about testing and design were the most frequent for treatment devices.

Table 4.3: FDA's 1986 Requests for Additional Information by Type of Device

Requested information	Type of device		Overall
	Diagnostic	Treatment	
Revisions to labeling	20%	13%	16%
Predicate device	2	1	1
Intended use	6	7	7
Instructions for use	10	12	11
Components and design	13	29	21
Manufacturing process	2	5	4
Testing information[a]	26	20	23
Sample device	0	2	1
Other information	15	18	16
(Estimated number of submissions)	(2,163)	(2,563)	(4,726)

[a]Refers to testing information of any type, including clinical data.

The extent to which additional information was requested also varied by device classification and review determination. For classified devices, FDA requests for additional information predictably were made most frequently for devices in class III and least frequently for devices in class I. (See table 4.4.) Devices without classifications ("None" in table 4.4) had the highest percentage of requests for additional information. This should not be surprising given the fact that the reason most of these devices are deleted from review is that the manufacturer has failed to provide the requested information. FDA requests additional information least frequently for devices found substantially equivalent in 30 days or fewer. (See table 4.5.)

Table 4.4: FDA's 1986 Requests for Additional Information by Classification and Type of Device

Classification	Type of device		Overall
	Diagnostic	Treatment	
None	80%	58%	65%
Class I	33	19	27
Class II	41	46	44
Class III	67	49	51
Total	**45**	**44**	**45**
(Estimated number of submissions)	(2,163)	(2,563)	(4,726)

Table 4.5: FDA's 1986 Requests for Additional Information by Determination and Type of Device

Determination	Type of device		Overall
	Diagnostic	Treatment	
Substantially equivalent in ≤ 30 days	5%	13%	10%
Substantially equivalent in > 30 days	55	57	56
Substantially equivalent with restrictions	42	48	47
Deleted or withdrawn	91	86	88
Not substantially equivalent or unable to determine	23	37	35
Total	**45**	**44**	**45**
(Estimated number of submissions)	(2,163)	(2,563)	(4,726)

Reviewers indicated to us that the quality of submissions and the nature and extent of FDA requests for additional information are influenced to some degree by the characteristics of the manufacturer. For example, manufacturers with experience with prior notifications for the type of product under review are usually associated with better notifications, about which fewer questions are raised. Reviewers also indicated that new manufacturers without track records at ODE or established manufacturers who have not previously produced a particular device type are typically scrutinized more closely.

Manufacturer responses to FDA requests for additional information can take a variety of forms. (See Table 4.6 on page 65.) In addition to submitting the basic types of documents associated with a product, the manufacturer frequently responds to specific questions about his device or provides revisions to labeling as requested by FDA. If the manufacturer does not respond to a request for information within 30 days, the premarket notification is automatically deleted from FDA's roster of active files. This is the most frequent reason for FDA's not making a determination for a particular submission. The manufacturer must then resubmit the premarket notification prior to marketing the device.

Table 4.6:Contents of 1986 Supplemental Submissions for "New" and Comparison Devices

Supplement contents	"New" device[a]	Comparison device[a]
General information		
Advertising	3%	3%
Operating instructions	11	1
Package labeling	7	1
Picture or drawing	9	2
References or articles[b]	7	[c]
Other material[b]	15	[c]
Testing information		
Diagnostic devices	16	[c]
Treatment devices[d]		
Bench test	10	[c]
Animal test	2	[c]
Test protocol	1	[c]
Human test	2	[c]
Answers to specific questions	30	[c]
Revisions to labeling	14	[c]

[a]The "new" device is the subject of the notification; the comparison device is the device to which equivalence is claimed.

[b]Refers to information in the submission that does not necessarily pertain directly to the device under review.

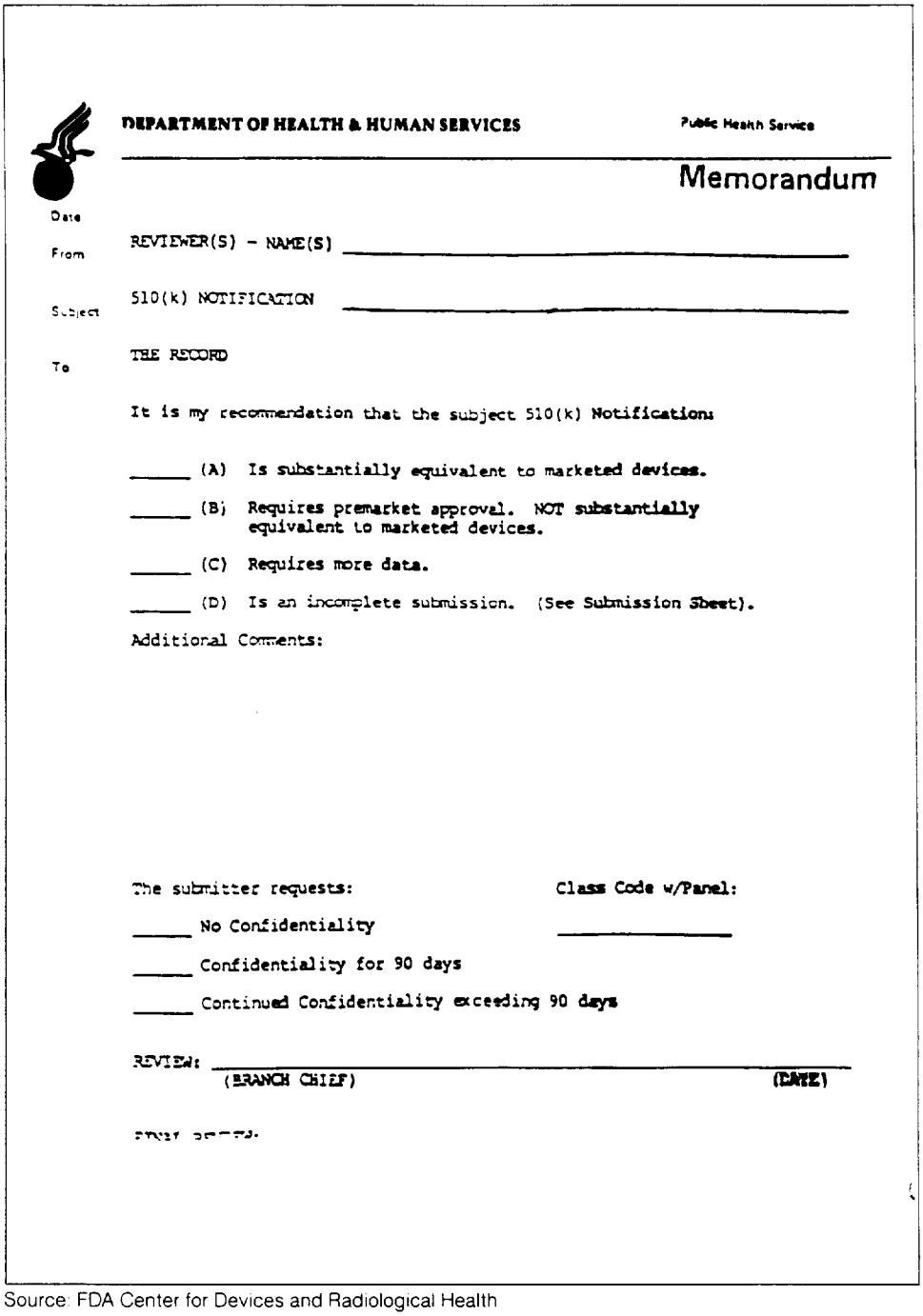
[c]Not applicable

[d]The category of treatment devices includes all devices that are not primarily diagnostic in function.

Final Decision-Making Process

Once the review is completed, the reviewer fills out a standard decision memo that contains a recommendation regarding the decision and, in the case of a "substantially equivalent" determination, assigns a product code and its associated classification to the device. (See figure 4.1.) The branch chief and division director then review the file and the recommended decision and sign the decision memo. As a matter of ODE policy, some decisions require additional review by the 510(k) coordinator, the Office of Compliance, or the associate director of ODE. In many cases, the only way to tell that these reviews were conducted is by the signature on the decision letter. In none of the files we examined were there notes taken at an internal meeting of FDA officials held to discuss a particularly complex decision (despite the fact that such meetings do occur).

Figure 4.1: Standard Decision Memo Used by FDA Reviewers



DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date

From REVIEWER(S) - NAME(S) _____

Subject 510(k) NOTIFICATION _____

To THE RECORD

It is my recommendation that the subject 510(k) Notification:

_____ (A) Is substantially equivalent to marketed devices.

_____ (B) Requires premarket approval. NOT substantially equivalent to marketed devices.

_____ (C) Requires more data.

_____ (D) Is an incomplete submission. (See Submission Sheet).

Additional Comments:

The submitter requests: Class Code w/Panel:

_____ No Confidentiality _____

_____ Confidentiality for 90 days

_____ Continued Confidentiality exceeding 90 days

REVIEW: _____
(BRANCH CHIEF) (DATE)

Source: FDA Center for Devices and Radiological Health

Adequacy of Implementation of Premarket Notification

We developed three criteria to evaluate the adequacy of FDA's day-to-day implementation of premarket notification. (They are implementation rather than outcome criteria; that is, they are yardsticks for measuring adequacy of day-to-day operations and do not deal with adequacy of results—a topic that is beyond the scope of this study.) The criteria are documentation of the review and decision in each case, the scientific background and training of reviewers, and consistency across similar types of devices in terms of information required and decisions made. We had hoped to apply an additional criterion to reflect the differential scrutiny of applications, based on the types of questions raised or by the class of device. However, as discussed in the following section of this report, the inadequate documentation in the files precluded our using this criterion.

Documentation

Adequate documentation of the ODE review process is important for at least three reasons. First, it is an essential part of the discipline and rigor that underlie the scientific process. As a process that relies on scientific judgment, the review of medical devices requires documentation to provide assurance that all relevant scientific issues were appropriately explored. Second, documentation provides the only means by which FDA and ODE management can monitor the review process and know whether their policies have been appropriately implemented. And third, documentation is the primary mechanism by which oversight of FDA by external agencies like GAO or the Inspector General can be exercised. This oversight is essential to guarantee FDA's public accountability.

FDA's documentation of the premarket notification process is very limited. (See table 4.7.) Contacts with manufacturers and other sources of information are documented at the discretion of the reviewers. The reasons for requesting specific information, the analysis of the submitted information, and the rationale for a particular decision are only infrequently documented in "reviewer's notes." In most cases, documentation is limited to a brief descriptive note on the standard form containing a recommendation regarding the appropriate determination. (See Fig. 4.1.) The management review of the recommendation can often only be inferred from the signature on the decision letter. As discussed earlier, none of the files reviewed contained notes taken at internal meetings of FDA officials in which complex policy decisions were made.

Table 4.7: 1986 Submissions Containing Reviewer Notes by Type of Device and Determination

Determination	Type of device		Overall
	Diagnostic	Treatment	
Substantially equivalent in ≤ 30 days	5%	6%	6%
Substantially equivalent in > 30 days	12	11	11
Substantially equivalent with restrictions	50	25	29
Deleted or withdrawn	8	11	10
Not substantially equivalent or unable to determine	85	84	84
Total	**11**	**12**	**11**
(Estimated number of submissions)	(2,163)	(2,563)	(4,726)

There are two situations when more documentation is included in a review file. First, when a decision that could be considered adverse by the manufacturer is made (that is, one in which the device is judged to be not substantially equivalent or substantially equivalent with restrictions), more of the files have reviewer's notes. For example, 84 percent of notifications found not substantially equivalent had reviewers' notes. Second, reviewers' notes are found in 20 percent of those submissions for treatment devices that contain test data. (See table 4.8.) Interviews with FDA officials indicated that these notifications may represent the more complicated questions of equivalence that require documentation in order for management to understand the rationale for the recommendation.

Table 4.8: 1986 Submissions Containing Reviewer Notes by Type of Device and Presence of Test Data

Contain test data	Type of device		Overall
	Diagnostic	Treatment	
No	10%	9%	9%
Yes	11	20	15
(Estimated number of submissions)	(2,163)	(2,563)	(4,726)

FDA management recognizes the need for more extensive documentation in premarket notifications and is currently considering how to accomplish it. The current plan is to have two levels of documentation: a low level for simple, "substantially-equivalent" determinations and a higher level for notifications in which significant issues are raised. However, they also point out that the failure to keep more adequate documentation partially results from manpower shortages and the need to allocate what personnel are available to more important tasks. The data on staff resources presented earlier partially supports this argument.

Reviewers' Backgrounds

The primary responsibility of reviewers in premarket notification is to determine the equivalence of a device described in a submission to a preamendment device on the basis of the scientific principles by which those devices operate and, as necessary, on the basis of comparative performance. Reviewers are neither expected nor required to make judgments about the clinical efficacy of the devices in making a determination of substantial equivalence. Rather, they have to take the preamendment device as a "given" and are concerned with the safety and effectiveness of the "new" device relative to that device. Because the reviewers' scientific judgement is the primary mechanism through which a substantial equivalence determination is made, their skill and training are important.

Education and Experience

FDA reviewers, in general, were found to have sufficient scientific background, training, and experience to review premarket notifications. Virtually all of the reviewers and branch chiefs had undergraduate degrees in a scientific field (98 percent and 100 percent, respectively); more than half of the reviewers (54 percent) and 85 percent of the branch chiefs also had advanced degrees in a scientific field. Reviewers had an average of 5 years experience outside FDA in their fields and 4 years experience at ODE. The average branch chief had more experience both outside FDA and in ODE. (See table 4.9.)

Table 4.9: 1986 ODE Reviewer and Branch Chief Qualifications[a]

Qualifications	Reviewer		Branch chief		Overall	
Education						
Undergraduate science degree	98%	(60)[b]	100%	(13)	99%	(73)
Advanced science degree[c]	54	(59)	85	(13)	60	(72)
Experience						
Median years at FDA (other than ODE)	3 years	(45)	7 years	(8)	4 years	(53)
Median years at ODE	4 years	(30)	5 years	(6)	4 years	(36)
Median years previous (non-FDA) experience	5 years	(47)	10 years	(10)	5 years	(57)

[a]We obtained at least partial information on 63 lead reviewers and 16 branch chiefs.

[b]The number in parenthesis indicates the number of individuals for whom we had the information indicated. There were some individuals with missing data in each category.

[c]This category includes M.S., Ph.D., M.D., D.D.S., and D.V.M., but does not include those who have advanced degrees in non-scientific fields (for example, business administration) or those who have credit hours toward advanced degrees.

Training

FDA management indicated that they attempt to provide staff with opportunities for additional education and relevant experience within the constraints imposed by resources and workload. In several divisions, new reviewers are given no submissions of their own to review. Rather, they work with the branch chiefs and more experienced reviewers until they have gained adequate experience. (One branch chief indicated that it took at least a year for a reviewer to gain adequate experience.) In all divisions, new reviewers were given fewer review responsibilities and closer supervision by the branch chief until they gained adequate experience.

FDA indicated that reviewers also take courses at colleges and universities that lead to advanced degrees or enroll in specialized courses such as those given by the Food and Drug Law Institute. In addition, they attend seminars and workshops given for ODE by academic researchers and the medical-device industry as well as meetings of National Institutes of Health study sections. For example, two ODE employees spent fiscal year 1986 in full-time academic study, and two other employees spent the year in a management training course. In fiscal year 1986, ODE staff prepared six articles for publication in professional journals and made 21 presentations at professional and trade association meetings.

Consistency

We are using the term consistency, in this context, to refer to our expectation that similar information will be required when similar issues about similar devices are raised or that the same determinations will be made across similar devices with similar information. If a lack of consistency across ODE divisions were discovered, it could signal a problem in the implementation of policies and procedures governing the review of applications. However, the lack of documentation in individual files prevented us from addressing the consistency issue from this point of view. Therefore, with one exception, the information we do present on consistency is indirect and should be interpreted cautiously.

Variations Across Divisions

One indirect approach to examining the issue of consistency is to look at variations across the organizational units within ODE. To the extent that decisions are being guided by a common policy, variations could indicate areas in which the divisions are interpreting the policy differently. However, as we point out below, it could also be due to legitimate differences between the divisions.

There were variations across divisions on several measures we examined. (See table 4.10.) The extent to which specific divisions requested additional information varied from a low of 32 percent in the Division of Surgical and Rehabilitation Devices to a high of 66 percent in the Division of Gastroenterology and Urology and General Use Devices. The percent of "not substantially equivalent" determinations varied across divisions from a low of 0 percent in the Division of Ophthalmic Devices and the Division of Clinical Laboratory Devices to a high of 4 percent in the Division of Anesthesiology, Neurology, and Radiology Devices. The percent of deleted or withdrawn submissions also varied across divisions from a low of 5 percent in the Division of Ophthalmic Devices to a high of 14 percent in the Division of Anesthesiology, Neurology, and Radiology Devices. Finally, one percent of notifications reviewed by the Division of Ophthalmic Devices had clinical data, while 4 percent of the submissions reviewed by the Division of Surgical and Rehabilitation Devices had some clinical data.[5]

[5]In developing our form for extracting information from individual premarket notification files, we decided to limit our examination of clinical testing of human subjects to treatment devices. We did this because testing of the accuracy, sensitivity, and other parameters of clinical laboratory (that is, diagnostic) devices are typically carried out on samples (for example, blood or urine) rather than directly on the patient in a manner that would expose the patient to risk. In other words, we chose to limit our discussion of "clinical testing" to situations in which identifiable patients (or groups of patients) were exposed to a treatment or procedure. As a result, we only identify the submission of clinical data for treatment devices.

Table 4.10: Variations Across ODE Divisions (1986)

ODE division	Request for additional information	NSE or UD[a]	Deleted or withdrawn	Inclusion of clinical data
Anesthesiology, Neurology, and Radiology Devices (507)[c]	55%[b]	4%	14%	3%
Cardiovascular Devices (648)	50	1	9	3
Clinical Laboratory Devices (1320)	42	0	9	[d]
Gastroenterology and Urology and General Use Devices (559)	66	1	13	4
Ophthalmic Devices (205)	33	0	5	1
Obstetrics and Gynecology, Ear, Nose, Throat, and Dental Devices (571)	38	2	13	4
Surgical and Rehabilitation Devices (917)	32	3	9	4
Total (4726)	**45**	**2**	**10**	**3**

[a]"Not substantially equivalent" (NSE) decisions and decisions where FDA is "unable to determine" (UD) whether the device is substantially equivalent

[b]Tabled values refer to percent of all premarket notifications reviewed by the division.

[c]Numbers in parenthesis refer to the estimated number of premarket notifications reviewed by the division in 1986.

[d]Not applicable

As previously indicated, it is difficult to infer the meaning of these variations across divisions. Variation across divisions would be expected for a number of reasons, including the following:

- Devices in the three classes require different levels of review due to the greater importance of performance data in assessing safety and effectiveness in classes II and III. Divisions with a greater proportion of devices in classes II or III might request more additional information or make more not-substantially-equivalent determinations.
- Variation in the number and experience of manufacturers making particular types of devices will require different divisions to engage in different regulatory efforts to achieve the same results. Divisions reviewing a greater proportion of devices produced by manufacturers who have recently entered the field may request more additional information than divisions reviewing a greater proportion of devices produced by a few well-established manufacturers.

- The number of complex versus simple devices a division reviews could cause variation across divisions. Divisions reviewing a greater proportion of devices that are technologically complex may need more additional information or have more not-substantially-equivalent determinations than divisions reviewing a greater proportion of technologically simple devices.

Thus, it is difficult to know when variation across divisions indicates a lack of consistency in reacting to similar circumstances and when it is the result of divisions reacting appropriately to differing circumstances. In any case, discovering variations such as these does provide a starting point for evaluating the reasons underlying the variations.

ODE-Wide Coordination

A second approach to examining the issue of consistency is to look at how issues that cut across the divisions of ODE are handled. For example, ODE has issued three separate guidance memos for all divisions to implement. The day-to-day implementation of the guidance on determinations of substantial equivalence is difficult to assess because of the lack of documentation. The memo delegating sign-off authority has been implemented in similar fashion by each of the divisions. However, the memo defining levels of review for class I devices has not been uniformly implemented by the various divisions.

A second area in which we observed ODE-wide coordination efforts was in the setting of policy on important scientific and technological questions. For example, ultrasound and laser-device premarket notifications are regularly reviewed by one of several divisions, depending on the manufacturer's claims concerning intended uses. In this case, clear interdivisional policy regarding the review of these devices had been developed and followed. We also found a case in which two divisions disagreed over the handling of a premarket notification involving a collagen. The issue was resolved in a meeting with the associate director of ODE.

However, we also found an example in which the divisions should have been following a similar policy, but were not. In reviewing the files, we found two virtually identical products (that is, same materials, same manufacturer, similar intended use) that had been reviewed in different divisions with very different outcomes. In one division, the manufacturer was required to provide data to validate the outcome of the sterilization procedure to be used in the manufacturing process. The submission was deleted by FDA when the data were not provided. (The

manufacturer sent only a description of the sterilization procedure.) In the other division, the device was found "substantially equivalent" after the manufacturer provided documentation of the procedure that would be used for sterilization.

In discussing this situation with reviewers in most of the divisions, we discovered that there was general agreement that both submissions should have been handled in the same way. In addition, we were told that there was an ODE-wide toxicology committee that set policy in the sterilization area. However, the reviewers had very different views on what the current policy was. This suggests to us that ODE management needs to pay more attention to identifying crosscutting scientific issues, setting consistent policy, and disseminating the relevant information to reviewers.

Specific Issues in Premarket Notification

Are Too Many Submissions Found Substantially Equivalent?

Some observers have suggested that the high percentage of premarket notifications found substantially equivalent means that FDA has not adequately scrutinized the submissions. This suggestion might appear reasonable based on the fact that 98 percent of those submissions for which FDA made a determination in 1986 were found substantially equivalent. However, when one considers the total number of submissions which FDA receives, and not just the ones for which a determination was made, a smaller percentage (85 percent) were found substantially equivalent. Ten percent were withdrawn (by the manufacturer or sponsor) or deleted (by FDA) without a determination being made; 2 percent were found not substantially equivalent; and the remaining 3 percent had a variety of other decisions (for example: not a device, transitional device, exempt class I device—among others). Of those devices found substantially equivalent, 3 percent had restrictions imposed on their use.

Within the group found substantially equivalent, there are subgroups of devices that most observers would agree are relatively innocuous and pose little risk to the public. Determinations that these devices are substantially equivalent should be expected and raise little controversy. For

example, 22 percent of all submissions are for class I devices and therefore, by definition, are unlikely to raise many difficult safety and effectiveness questions. In addition, another 19 percent of premarket notifications for non-class-I devices were found substantially equivalent within 30 calendar days and thus were viewed by FDA as raising few safety and effectiveness questions and posing few risks to the public.[6]

If one regards these submissions (41 percent of all submissions) as necessary but unlikely to raise any significant questions about the appropriateness of FDA's decisions, then the percentage of all submissions found substantially equivalent and presenting important issues for a determination of substantial equivalence is reduced to approximately 44 percent (that is 85 percent minus 41 percent). When viewed in the context of the 12 percent of all notifications that are deleted, withdrawn, or found not-substantially-equivalent, the percent of submissions with significant issues that are subsequently found substantially equivalent is less startling.

Conversely, the fact that 41 percent of notifications present very few questions and require little review raises the issue of whether FDA should even receive notifications for those devices. As noted earlier, FDA is already moving to exempt more class I devices from premarket notification and to place more class II devices into class I. In addition, the Premarket Notification Criticism Task Force recommended some changes in the types of device modifications that require premarket notifications, suggesting instead that Good Manufacturing Practices inspections be used as a mechanism for tracking such changes. FDA has noted, however, that there may be a deterrent effect associated with premarket notification that serves to protect the public health. Furthermore, premarket notification assists FDA in monitoring changes in medical devices and in the device industry.

Is FDA Conducting Mini-PMAs?

According to some observers, FDA has been avoiding the more resource-intensive, and public, premarket approval process by conducting "mini-PMAs" or "hybrid 510(k)s" within the less resource-intensive premarket notification process. This is an issue for two reasons. First, it might indicate that FDA is not implementing the amendments in the manner in which the Congress intended. Second, it raises questions about

[6]There are other categories of devices that could be included in this group. For example, while diagnostic test kits used in clinical laboratories cannot be considered risk-free (that is, there are questions concerning accuracy and reliability, among others), the issues involved in evaluating their performance are relatively straightforward, and their appropriate use poses no immediate risk to the patient.

whether premarket notification can provide the same level of public protection that premarket approval does through the use of expert panels and public comment.

The primary observations cited in support of the argument that FDA is conducting "mini-PMAs" are the extent of testing information required by FDA and the type of testing information requested. First, it is argued that FDA is requiring more testing information, including clinical testing, than should be required to demonstrate substantial equivalence. Second, it is argued that the very fact of requiring clinical data creates at least the appearance that PMA-like reviews are being conducted. The special significance that is attached to clinical testing arises from the language of the statute, which specifically calls for "well-controlled clinical studies" to be conducted in premarket approvals.

The rationale that FDA uses for requiring clinical data within premarket notification was discussed in Chapter 3. We indicated there that FDA's approach, if implemented correctly, would result in a reasonable distinction between the use of clinical data in a premarket notification and its use in a premarket approval. Given the lack of documentation in the files, we cannot begin to assess the extent to which the policy has been implemented as intended.

We can provide information on the extent to which FDA receives clinical and other testing data in premarket notification submissions. We can also make some observations in regard to when clinical data were requested. However, linking the submission of clinical data to a specific FDA request for clinical data is very difficult. For example, FDA can and does request clinical data that the manufacturer has not yet collected. In those cases, the notification will be withdrawn or deleted and resubmitted later. The later notification may or may not make reference to the earlier submission and the FDA request.

Five percent of submissions for treatment devices contained clinical data. (See table 4.11 on page 77.) Sixteen percent of the notifications found not-substantially-equivalent contained clinical data, as did 1 percent of deleted or withdrawn applications and 8 percent of the submissions found substantially equivalent in over 30 days. Of the 5 percent of submissions with clinical data, 26 percent were in class III, 52 percent in class II, and 11 percent in class I; 11 percent were not classified.

Table 4.11: 1986 Submissions by Determination, Type of Device, and Type of Test Data

	Diagnostic device		Treatment device		Overall	
Determination	**Clinical**	**All types**	**Clinical**	**All types**	**Clinical**	**All types**
Substantially equivalent in ≤ 30 days	[a]	38%	0%	16%	[a]	25%
Substantially equivalent in > 30 days	[a]	58	8	38	[a]	49
Substantially equivalent with restrictions	[a]	33	7	39	[a]	38
Deleted or withdrawn	[a]	25	1	18	a	21
Not substantially equivalent or unable to determine	[a]	38	16	41	a	41
Total	[a]	**49**	**5**	**29**	[a]	**38**
(Estimated number of submissions)		(2,163)		(2,563)		(4,726)

[a]Not applicable

In most cases involving clinical data, the data were supplied by the manufacturer in the initial notification, although FDA might have requested it in an earlier application. The data usually were aggregated across a series of patients on whom the device had been tested. Only one trial with random assignment was reported. Finally, in examining the 48 deleted or withdrawn notifications in which FDA had requested additional testing information, we found that specific clinical testing information was explicitly requested for only 12.5 percent of those submissions.

Summary and Conclusions

The organizational structure for reviewing premarket notifications is established and provides for efficient management of the administrative aspects of the process. The actual review of premarket notifications revolves around the branch chiefs. They are responsible for initial prereview of submissions, assignment of a reviewer, assisting reviewers in determining the need for additional information from the manufacturer, implementing divisional and ODE policy, training new reviewers, and reviewing recommendations on determinations of substantial equivalence. The review itself depends on the scientific judgment of the reviewer, who is guided by ODE policies on what constitutes substantial equivalence.

We examined the adequacy of FDA's review of premarket notifications in terms of three criteria: documentation, reviewer education and experience, and consistency. First, we judged the level of documentation to be inadequate, particularly for substantially-equivalent determinations (although it did improve as the decisions became more complex or, from

the point of view of the manufacturer, more adverse). FDA has recognized the need for improved documentation and is planning to make improvements in this area. Second, reviewers were found, on the average, to have the scientific backgrounds, training, and experience necessary to review premarket notifications. Finally, to improve its review process in the area of consistency, we believe that FDA needs to better identify important scientific issues that cut across divisions, establish ODE-wide policies, and disseminate those policies to the reviewers.

Answering the question of whether FDA finds too many devices substantially equivalent cannot be done in a straightforward way. The suggestion by some that finding 98 percent of notifications substantially equivalent is indicative of a problem is misleading for two reasons. First, the 98 percent figure is based only on those notifications for which FDA rendered a final determination. Among all notifications, regardless of their final dispositions, 85 percent were found substantially equivalent in 1986. Second, 41 percent of those notifications found substantially equivalent were notifications concerning which few experts would question FDA's determinations. FDA is moving to exempt more class I devices from the 510(k) requirements, which will lessen the influence of relatively safe devices on the overall statistics. Concerning the "mini-PMA" question, there is little evidence that FDA is conducting "mini-PMAs" in any substantial proportion of cases. Only 5 percent of notifications for treatment devices contained any clinical data at all, and some of that may have been submitted without any FDA requirement.

Recommendations

We recommend that the secretary of the Department of Health and Human Services instruct the commissioner of FDA to establish a requirement that written documentation of the review and decision-making process be included in each premarket notification file. The extent of documentation should vary depending on the seriousness of the questions raised during the review.

Adequate documentation of the review process is important for at least three reasons. First, it is an essential part of the discipline and rigor that underlies the scientific process. Second, documentation provides a means by which FDA and ODE management can monitor the review process. Third, documentation provides one of the chief means by which oversight of FDA by monitoring bodies like GAO or the Office of Inspector General can be exercised.

Simple notifications that do not depart from a straightforward path through the flowchart could easily be documented with a checkoff to that effect on a standard form. Any departures from that simple substantially-equivalent determination should be more fully documented. Documentation should indicate what questions were raised during the review, how they were resolved, and how the decision was reached. Such documentation could then be referenced in similar future notifications, thus decreasing the overall burden over time.

We recommend that the secretary of the Department of Health and Human Services instruct the commissioner of FDA to develop and implement processes, first for identifying scientific issues that require uniform treatment across the divisions of ODE, then for developing policies, and finally for ensuring that these policies are implemented in the review of premarket notifications.

Although some crosscutting issues have been identified by FDA and ODE-wide policies subsequently formulated and disseminated to reviewers, we found several situations that suggest that more coordination efforts are needed. For example, the ODE policy on how premarket notifications for class I devices should be reviewed by the branch chiefs is not being implemented uniformly across the divisions. In addition, the sterilization-validation case we discuss in chapter 4 suggests that more attention to coordination is needed. FDA is in the best position to determine the administrative process most appropriate to their unique needs.

Agency Comments

FDA concurred with each of these recommendations. (See appendix V.) Their comments include a description of the improvements they propose to make in response.

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Review of FDA Premarket Notification Data

Premarket Notification Data Base

In December of 1986, FDA supplied us with computer tapes containing data on all premarket notifications submitted to FDA since the implementation of the provisions in 1976. One tape contained a limited set of facts on each submission (such as document number, document type, supplement number, date of receipt, status, decision, decision date, request for information date, information due date, product code, and medical specialty panel code). The second tape contained the information needed to translate the three-letter product code into a verbal description and determine the class of the device. Because the original data tape did not contain full information for all the calendar 1986 submissions, a more complete set of data for the 1986 submissions was substituted from an FDA-supplied computer tape in August 1987.

The data were organized with a separate record for each submission by a manufacturer to FDA, including any submissions of requested additional data (termed supplements). The data were first aggregated so that each record represented the review of a single device as well as all supplements. This file was then matched to the classification data to obtain the class of each device, based on the product code assigned to the device. The final file, used for analyses, contained the following variables: document number, class, product code, number of supplements, date the original submission was received (month, day, and year), decision, and calender time to make a decision.

There were some problems with the data. Many cases did not have a classification match. Most of these were either for not-substantially-equivalent decisions or for cases that were withdrawn or deleted. However, classification matches were missing for some substantially-equivalent decisions as well. The calculation of calendar time to decision indicated that there are some errors in recording submission dates and decision dates. There also appeared to be a practice of recording the original submission date as the decision date for a relatively large number of applications (over 1,300). This occurred almost exclusively for withdrawn and deleted files.

As a result of these problems, we limited our use of these data to looking at changes over time in the number of submissions, in the primary decisions, and in the percent of devices found substantially equivalent that fell into the different classes.

Review of Premarket Notification Files

Sampling Plan

We used information on the dates of submission and decision, type of decision, and device classification to develop a sampling plan. For two reasons, we chose as the universe all applications with a 1986 submission date. First, a full year was needed to provide a large enough group of not-substantially-equivalent decisions to conduct meaningful analyses. Second, formal guidance on reviewing premarket notifications was issued to FDA reviewers in June 1986. Looking at applications over the full year would provide an opportunity to examine changes in decisions, review times, and other factors that might be associated with the new guidance.

Three factors were represented in the original sampling plan. First, we wanted to be able to characterize any differences in the applications or their review that were related to the decision. Several different codes were available to describe the decisions. An examination of the descriptions of the codes as well as the distribution of decisions suggested that four different decision groups should be examined: (1) not-substantially-equivalent, (2) withdrawn or deleted, (3) substantially-equivalent-with-restrictions, and (4) substantially-equivalent. (See table II.1 on page 84.)

Table II.1: Population of Premarket Notifications (1986)

Strata	Number
Not substantially equivalent	77
Withdrawn or deleted	489
Substantially-equivalent with restrictions	130
Substantially-equivalent	
Not classified	
No FDA request	241
FDA request	106
Class I	
No FDA request	833
FDA request	191
Class II	
No FDA request	1,596
FDA request	841
Class III	
No FDA request	125
FDA request	97
Other decisions	166
No decisions[a]	219
Total	**5,111**

[a]At the time that the sample was drawn, in early May, decisions on these notifications had not yet been made.

Second, because of the central role that the class of the device plays in its regulation, we wanted to represent the class of the device in our sampling plan. For two reasons, this was only possible for devices found substantially-equivalent. First, a device is only classified if it is found to be substantially equivalent to another device. Second, the overall number of notifications found substantially equivalent with restrictions was too small to allow for stratification by class of device.

Finally, because one of the main criticisms of FDA's implementation of premarket notification is the nature and extent of data they request from manufacturers, we wanted to be able to make statements about the types of information FDA was requesting from manufacturers. Therefore, we further divided the substantially-equivalent determinations into substrata composed of (1) those applications for which FDA requested no additional information and (2) those FDA had placed on hold pending the receipt of additional information from the manufacturer.

Original Sample. We decided to examine all not-substantially-equivalent determinations because of the small number of cases involved. Sample

sizes in the other groups are based on estimates of the proportion of cases in the various groups that we expected to contain information on safety and effectiveness. Our estimates were developed from the results of an earlier study of premarket notifications conducted by FDA which found that 11 percent of notifications contained some type of performance information.[1] We decided to use a slightly higher rate of 15 percent with a sampling error of ± 5 percent based on a 95 percent confidence interval. Because we had no basis on which to estimate the proportion of withdrawn or deleted cases that might have performance data, the sample size is based on a proportion of 50 percent with a sampling error of ± 6 percent. The sampling design was chosen to balance the need for precision with the available resources for reviewing files. The original sample sizes are shown in table II.2.

Table II.2: Original Sample of Premarket Notifications (1986)

Strata	Sample size
Not-substantially-equivalent	77
Withdrawn or deleted	177
Substantially-equivalent with restrictions	80
Substantially-equivalent	
Not classified	
No FDA request	125
FDA request	73
Class I	
No FDA request	195
FDA request	108
Class II	
No FDA request	220
FDA request	196
Class III	
No FDA request	80
FDA request	71
Total	**1,402**

Revised Sample. During the development and final testing of our data collection instrument, a decision was made to revise our original sampling plan for two reasons. First, in the course of testing the instrument, we became aware that FDA did not always place a file on hold when they made a request for additional information. Second, our estimates of the time needed to code individual applications indicated that coding the

[1]C. F. Blozan and S. A. Tucker, "Premarket Notifications: The First 24,000," Medical Devices and Diagnostics Industry, January 1986.

original sample would require more than our available resources. We therefore decided to eliminate the stratification based on requests for additional information. The sample sizes (shown in table II.3) were chosen to keep the overall sampling errors at the same levels as in the original sample.

Table II.3: Revised Sample of Premarket Notifications (1986)

Strata	Revised sample	Achieved sample
Not-substantially-equivalent	77	95
Withdrawn or deleted	177	175
Substantially-equivalent with restrictions	80	79
Substantially-equivalent		
Not classified	135	135
Class I	204	203
Class II	230	229
Class III	90	90
Total	**993**	**1,006**

[a]Includes unable-to-determine decisions

During coding, we found that FDA had used the code "unable to determine" in essentially the same way as "not substantially equivalent." Therefore, because the sampling plan called for reviewing all not-substantially-equivalent submissions, the 17 unable-to-determine submissions were included with the not-substantially-equivalent submissions.[2] At the completion of coding, only 5 of the 993 notifications selected as part of the revised sample (.5 percent) could not be located (2 withdrawn or deleted; 1 substantially equivalent with restriction; 1 substantially equivalent, Class I; 1 substantially equivalent, Class II). The achieved sample is shown in table II.2.

Development of Data Collection Instrument

A data collection instrument was developed for coding the relevant information from the premarket notification applications. The information extracted included the type of device (according to class, manufacturer, and common and proprietary name); the information provided in the original application (such as package labeling, instructions for use, package insert, advertising, testing results, and catalogs); the information that FDA requested (for example, revisions to labeling, testing,

[2]On account of the passage of time between when the sampling was done and when we reviewed files and added the unable-to-determine decisions, the final achieved group was larger than the original population.

instructions for use, and samples); the information submitted by the manufacturer in response to the FDA request; and documentation of FDA's review and decision. (See appendix III.)

After an initial draft of the data collection instrument was developed, it was tested on a small number of applications and revised. The testing and revision process required several iterations before a final draft was ready for reliability testing. Minor changes to the form and some specific coding conventions were developed during the course of reliability testing. All four coders were trained until they attained acceptable levels of reliability. Their reliability was checked again after half of the sample was coded, and it had remained at an acceptable level.

Data Collection Instrument

DCI1: TYPES OF INFORMATION IN 510K[a]

1. CODER: _____ DATE: _____ TIME BEGIN: _____

2. INFORMATION FROM 510(K) DATA SYSTEM(IF DISCREPENCY, CHECK "NO" AND RECORD INFORMATION FROM FILE)

	YES	NO
DOCNUM	( )	( )
LOGIN DATE	( )	( )
PRODCODE	( )	( )
CLASS	( )	( )
N/SPLMNTS.	( )	( )
DECISION	( )	( )
TIME DECIDE	( )	( )

3. SIGNER OF DECISION LETTER _____

4. FDA REVIEWER NAME _____

	YES	NO
5. MORE THAN ONE REVIEWER?	( )	( ) 91.6(2.0)
6. REVIEWERS' NOTES?	( )	( ) 88.6(2.1)
IF YES, HOW MANY PAGES_____		
7. DIAGNOSTIC DEVICE?	( )	( ) 54.2(3.5)

8. OTHER 510(K)'S CITED? _____

9. FDA REQUEST FOR SUPPLEMENTAL INFORMATION	( )	( ) 55.5(3.4)
IF YES, WAS FILE PLACED ON HOLD	( )	( ) 64.7(3.3)
NATURE OF REQUEST:		
10. REVISIONS TO LABELING	( )	( ) 83.9(2.5)
11. PREDICATE DEVICE	( )	( ) 98.9(0.7)
12. INTENDED USE	( )	( ) 93.3(1.6)
13. INSTRUCTIONS FOR USE	( )	( ) 88.8(2.1)
14. DESIGN OR COMPONENTS	( )	( ) 78.6(2.8)
15. MANUFACTURING PROCESS	( )	( ) 96.0(1.4)
16. TESTING INFORMATION	( )	( ) 77.2(2.8)
17. SAMPLE	( )	( ) 99.2(0.3)
18. OTHER	( )	( ) 83.7(2.5)

SPECIFY _____

[a]The numbers inserted into the data collection instrument are the percent of files that do not contain that item and the associated sampling error.

1

MATERIALS SUBMITTED BY MANUFACTURER AS SUPPLEMENT

	FOR TARGET DEVICE		FOR COMPARISON DEVICE	
	YES	NO	YES	NO
19. ADVERTISING/BROCHURES		96.6(1.4)		97.1(1.2)
20. OPERATING MANUALS/ INSTRUCTIONS FOR USE/ PACKAGE INSERT		88.9(2.3)		98.0(0.6)
21. PACKAGE LABELS		93.0(1.9)		99.3(0.5)
22. DRAWING/PHOTOGRAPHS OF DEVICE OR PACKAGE CONTENTS		90.6(2.1)		98.3(0.9)
23. JOURNAL ARTICLES/REFERENCES (ANY RELEVANT CITATION)		93.2(1.7)		
24. OTHER MATERIAL		84.7(2.6)		

SPECIFY _____

FOR DIAGNOSTIC DEVICES

25. COMPARATIVE DATA ON ACCURACY, PREDICATIBILITY, ETC		92.8(1.9)

FOR OTHER DEVICES

26. BENCH/QUALITY ASSURANCE TESTS		94.3(1.6)
27. ANIMAL TESTS		98.8(0.8)
28. PROTOCOLS FOR HUMAN TESTS		99.7(0.4)
29. COMPLETED HUMAN TESTS		99.0(0.8)
30. ANSWERS TO SPECIFIC FDA QUESTIONS		70.1(3.3)
31. REVISIONS TO LABELING AS REQUESTED BY FDA		86.5(2.5)

MATERIAL SUBMITTED BY MANUFACTURER IN ORIGINAL SUBMISSION

32. MANUFACTURER NAME: _____

33. DEVICE NAME (COMMON) _____

(PROPRIETARY) _____

	YES	NO	
34. REGISTRATION NUMB.....	( )	( )	17.8(2.6)
35. DEVICE CLASSIFICATION.....	( )	( )	28.0(3.1)
36. SAMPLE DEVICE.....	( )	( )	97.4(1.0)

	FOR TARGET DEVICE		FOR COMPARISON DEVICE	
	YES	NO	YES	NO
37. ADVERTISING/BROCHURES.....	( )	( ) 66.8(3.3)	( )	( ) 71.0(3.3)
38. OPERATING MANUALS/ INSTRUCTIONS FOR USE/ PACKAGE INSERT.....	( )	( ) 34.8(3.3)	( )	( ) 79.1(3.0)
39. PACKAGE LABELS.....	( )	( ) 32.7(3.3)	( )	( ) 90.0(2.1)
40. DRAWING/PHOTOGRAPHS OF DEVICE OR PACKAGE CONTENTS.	( )	( ) 51.0(3.5)	( )	( ) 77.7(3.0)
41. JOURNAL ARTICLES/REFERENCES.. (ANY RELEVANT CITATION)	( )	( ) 66.6(3.4)		
42. OTHER MATERIAL	( )	( ) 67.2(3.4)		

SPECIFY _____

FOR DIAGNOSTIC DEVICES

43. COMPARATIVE DATA ON ACCURACY, PREDICATIBILITY, ETC.....	( )	( ) 79.8(3.0)

FOR OTHER DEVICES

44. BENCH/QUALITY ASSURANCE TESTS(	)	( ) 89.4(2.0)
45. ANIMAL TESTS.....	( )	( ) 98.1(0.9)
46. PROTOCOLS FOR HUMAN TESTS....	( )	( ) 99.7(0.4)
47. COMPLETED HUMAN TESTS.....	( )	( ) 97.8(0.9)

3

48. COMMENTS _____

48. TIME END _____

Coding Instructions for Data Collection Instrument

1. Coder: GAO reviewer of FDA files.[1]

Date: Date file reviewed.

Time begin: Time file review started.

Information From 510(k) Data System

2. Information from 510(k) data system: Check "NO" if file information is discrepant from information from FDA's data system that includes the following:

- K-Number: Unique identifier assigned to each manufacturer's submission.
- Log-in data: Date submission is logged in by FDA as received.
- Device type: Three letter FDA code indicating type of device.
- Device class: Regulatory class of device assigned by FDA.
- No. of supplements: Number of information supplements to the original submission.
- Decision: FDA's "substantial equivalence" decision.
- Time to decide: Only check to be sure that the time is roughly the same.

FDA Review Information

3. Signer of FDA decision letter: FDA official who signs the letter to the manufacturer giving FDA's decision.

4. FDA reviewer name: FDA submission reviewer or reviewers.

5. More than one reviewer: Indication in decision memo or elsewhere that there was more than one reviewer for the submission.

6. Reviewer's notes: In coding information about FDA review, the decision letter and decision memo should not be coded. The category of reviewer notes should include more than a simple description of the file, device, or phone conversation. It should include some analysis of the decision-making process. Anyone providing an opinion about the 510(k), such as an outside reviewer, should be considered a "reviewer." Memos recording FDA telephone contacts with manufacturers should be treated under the requests for information section.

7. Diagnostic device: Indication that the primary purpose of the device is diagnostic.

[1]Numbers correspond to sections (lines) on the data collection instrument in appendix III.

8. Other 510(k)'s cited: Indication that device had been assigned another K-number at some other time; comments are to give the previous K-numbers and the circumstances that required another K-number.

FDA Request for Supplemental Information

9. FDA request for supplemental information: Indication that FDA requested supplemental information. Supplemental information which FDA did not request will be coded as "supplemental." Code "YES" for HOLD only if there is an explicit statement occurring in a letter from FDA to the manufacturer that the submission was put on HOLD pending receipt of requested information.

10. Revisions to labeling: Indication that FDA has required some revision to the label, advertising material, or package insert. Requests that the labels be sent should be coded under "Other."

11. Predicate device: Request by FDA for preamendments device to which the current device is to be compared. This does not include comparative devices designated as "currently marketed devices." Code comparative devices as "Other" and specify.

12. Intended use: "Intended use" refers to the specific situations in which the device will be used. "Instructions for use" should be used to refer to questions about the specific instructions for using the product that are (or should be) included in the operating manual or package insert.

13. Instructions for use: "Instructions for use" should be used to refer to questions about the specific instructions for using the product that are (or should be) included in the operating manual or package insert.

14. Design or components: FDA questions about the design or components of the device under review.

15. Manufacturing process: FDA questions about the process used to manufacture the device.

16. Testing information: FDA requests that testing information be submitted on the device.

17. Sample: Indication of FDA request for a sample of the device.

18. Other: FDA request for other supplemental information. Specify what additional information was requested such as comparative devices designated as "currently marketed devices."

Materials Submitted by Manufacturer as Supplement

19. Advertising or brochure: Material describing a device that was primarily prepared for sales purposes rather than for a 510(k) submission. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

20. Operating manuals, instructions for use, package insert: Instructions that would be contained inside the package and that indicate either how the device is to be operated or how and when the device is to be used. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

21. Package labels: Depiction (draft or actual) of the label that will actually be on the device or device's package. (This does not include warnings or statements of limitations found in operating manuals.) A picture of the device on an advertising brochure should not be coded as a package label unless the label is clear and readable. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

22. Drawing or photographs of device or package contents: Depiction of device or package contents. (If verbal description is also given, then code description and drawing or photograph. A picture of the device on an advertising brochure should not be coded as a package label unless it is clear that the label is reproduced in the brochure and the label is clear and readable. When coding material in the original cover letter and

attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

23. Journal articles and references: If articles are provided or cited, check "yes" for journal articles and references. (This includes reference lists in package inserts.) When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

24. Other material: Other material included in the supplemental submission besides that included in list. When coding supplemental material, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information. Code tests of accuracy, sensitivity, and other aspects of diagnostic tests here. Reserve the "testing information" category for comparisons of tests of two devices.

25. Comparative data on accuracy, predictability, and other factors: Results or references to testing of diagnostic devices that indicate the current device was compared to another device or standard reference method. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

26. Bench or quality assurance tests: Test conducted on the device by laboratory or manufacturing personnel in which prototype is used; or test in which measurements are made of a series of devices after they are produced for the purpose of insuring that the manufacturing process is producing "good" devices. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or

picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

27. Animal tests: Tests (studies) in which the device is used in animals under conditions as similar as possible to those in which the device will be used in humans. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

28. Protocols for human testing: Guidelines on how tests with humans are to be conducted, for example, what kind of subjects, how many, under what circumstances. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

29. Completed human tests: Trials in which the device was used on human subjects. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

30. Answers to specific FDA questions: Indication that FDA asked specific questions of the manufacturer that were answered. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

31. Revisions to labeling as requested by FDA: Indication that FDA has required some revision to the label. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as

part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

Material Submitted by Manufacturer in Original Submission

32. Manufacturer name: As listed on cover letter stationery.

33. Device name: Name of device indicated in the cover letter.
Common name: Name indicated in the cover letter as the common name.

Proprietary name: Name indicated in the cover letter as the registered manufacturer's name.

34. Registration number: Manufacturer's number assigned by FDA. If the manufacturer either provides a registration number or acknowledges the requirement to obtain one prior to marketing, code "yes" for registration number.

35. Device classification: Regulatory class of device assigned by FDA.

36. Sample device: Indication in cover letter that a sample of the device was included in the submission.

37. Advertising or brochure: Material describing a device that was primarily prepared for sales purposes rather than for a 510(k) submission. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

38. Operating manuals, instructions for use, or package insert: Instructions that would be contained inside the package and that indicate either how the device is to be operated or how and when the device is to be used. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

39. Package labels: Depiction (draft or actual) of the label that will actually be on the device or device's package. (This does not include warnings or statements of limitations found in operating manuals.) A picture of the device on an advertising brochure should not be coded as a package label unless the label is clear and readable. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

40. Drawing or photographs of device or package contents: Depiction of device or package contents. (If verbal description is also given, then code description and drawing or photograph.) A picture of the device on an advertising brochure should not be coded as a package label unless it is clear that the label is reproduced in the brochure and the label is clear and readable. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

41. Journal articles and references: If articles are provided or cited, check "yes" for journal articles or references. (This includes reference lists in package inserts.) When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

42. Other material: Other material included in the original submission besides that included in list. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information. Testing information on accuracy, sensitivity, and other aspects of a diagnostic device should be coded here unless it is compared to testing results on a comparison device. (See 43 below.)

43. Comparative data on accuracy, predictability, and other test factors: Results or references to testing that indicate the current device was compared to another device or some reference method. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

44. Bench or quality assurance tests: Test conducted on the device by laboratory or manufacturing personnel in which prototype is used; or test in which measurements are made of a series of devices after they are produced for the purpose of insuring that the manufacturing process is producing "good" devices. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

45. Animal tests: Tests (studies) in which the device is used in animals under conditions as similar as possible to those in which the device will be used in humans. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

46. Protocols for human testing: Guidelines for how tests with humans are to be conducted, for instance, what kind of subjects, how many, under what circumstances. When coding material in the original cover letter and attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

47. Completed human tests: Trials in which the device was used on human subjects. When coding material in the original cover letter and

attachments, treat all material as if it stood alone. For example, if a picture, drawing, or illustration of the device appears as part of the package insert or operating manual, check "yes" for "drawing or picture." The same is true for comparisons of specifications between devices, device tests, references, and other categories of information.

48. Comments: Written comments by coder that cover anything in file not specifically mentioned in DCI.

49. Time end: Time file review finished.

Recommendations of FDA's Premarket Notification Criticism Task Force

A. When Should 510(k) Submissions Be Made and How Should FDA Ensure Compliance With 510(k) Requirements?[1]

1. Adopt class I device exemption criteria which offer

- increased exemptions, with
- limits on exemptions and
- partial exemptions.

2. Establish a working group to change the 510(k) regulation so it distinguishes between GMP and 510(k) issues and allows less discretion for new intended uses.

3. Increase surveillance of first time manufacturers of a device, and of the highest risk device modifications, to ensure that 510(k) are being submitted when necessary.

B. How Can 510(k) Submissions Be Efficiently But Adequately Processed?

1. Implement the information system under development.

2. Complete and adopt a training plan and reviewer's manual.

3. Complete and install two new documentation systems:

- type A for routine reviews, and
- type B for reviewing testing data.

C. What Is the Meaning of Substantial Equivalence, and What Data Are Necessary to Reach a Decision?

1. Clarify that new devices will undergo premarket approval when they have a new use, when they are not as safe or effective as a preamendments device, when they pose new types of risks or questions about efficacy, or when it is not clear how to compare a new device's features to the features of a preamendments device. If this approach cannot be taken because of legal constraints, propose a legislative change that will overcome the legal obstacles.

[1]Food and Drug Administration, Center for Devices and Radiological Health, Report of the Premarket Notification Task Force (unpublished report, September 1985).

2. If the device can be marketed through the 510(k) process, collect performance testing data for new technological features. Although there may be legal constraints on the type of data required in a 510(k), all data necessary to establish substantial equivalence should be sought.

3. Require premarket approval applications for as many high priority class III preamendments devices as possible.

4. Develop a regulation describing the characteristics of effective, low-risk class I devices to expedite reclassification of such new devices.

Agency Comments

DEPARTMENT OF HEALTH & HUMAN SERVICES — Office of Inspector General

MAR 11 1988

Mr. Lawrence H. Thompson
Assistant Comptroller General
U.S. General Accounting Office
Washington, D.C. 20548

Dear Mr. Thompson:

Enclosed are the Department's comments on your draft report, "Medical Devices: Food And Drug Administration's 510(K) Policies Are Adequate But Operations Need Improvement." The enclosed 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'S DRAFT REPORT, "MEDICAL DEVICES: FOOD AND DRUG ADMINISTRATION'S 510(k) POLICIES ARE ADEQUATE BUT OPERATIONS NEED IMPROVEMENT," JANUARY 29, 1988

General Comments

Overall, the report is thorough and fair in its observations and judgments about the Food and Drug Administration's (FDA) performance in implementing the Medical Device Amendments. We generally agree with the criticisms and the ameliorating factors discussed in the report.

GAO Recommendation

We recommend that the Secretary of the Department of Health and Human Services instruct the Commissioner of FDA to:

--Establish a requirement that written documentation of the review and decisionmaking process be included in each premarket notification file. The extent of documentation should vary, depending on the seriousness of the questions raised during the review.

Department Comment

We concur. Although FDA has a long history of precedent decisions for most 510(k) reviews and experienced reviewers are thoroughly familiar with the reasons for specific decisions in these cases, documentation of the decisions could be improved. Given that FDA reviews approximately 5,000 510(k) notifications per year, the Agency must ensure that added documentation does not consume an inordinate amount of the reviewers' time and thereby create backlogs of unreviewed 510(k)'s. During 1988, FDA will take steps to improve the consistency and completeness of documentation while allowing reviewers sufficient flexibility to ensure that documenting decisions do not become overly burdensome.

GAO Recommendation

--Develop and implement a process for identifying scientific issues that require uniform treatment across the divisions of ODE, for developing policies, and for ensuring that the policies are implemented in the review of premarket notifications.

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Department Comment

We concur. Although FDA has achieved a high level of consistency in 510(k) reviews, more can be done. As noted by GAO, FDA has issued a compilation of policy statements (the Bluebook) covering all review processes for use by reviewers in making decisions that are consistent across division lines. The Office of Device Evaluation in FDA will institute periodic meetings of branch chiefs responsible for 510(k) reviews for the purpose of identifying and resolving cross-cutting issues. Since branch chiefs play a pivotal role in the 510(k) review process, we believe this action will be particularly effective in ensuring uniformity across divisions. Any new policies or procedures that are instituted as a result of these meetings, or from other activities, will be disseminated to the reviewers via updates to the Bluebook, mentioned above.

*U.S. G.P.O. 1988-201-749:80236

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