5.

Regulation of Medical Devices by the Food and Drug Administration

Hearts will never be practical until they can be made unbreakable.

—*The* ***Wizard of Oz***

Contents

LIST OF TABLES

FIGURES

5. Regulation of Medical Devices by the Food and Drug Administration

INTRODUCTION

The Medical Device Amendments of 1976 (Public Law 94-295) consolidated and expanded existing Federal authority over medical devices into a system of regulating the safety and effectiveness of medical devices in proportion to the degree of risk that they pose. In the past 2 years, interest in the law has grown because of problems that have surfaced in implementing some key provisions and because of concerns regarding the costs of some provisions relative to the incremental gains in safety and effectiveness.

The Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce held hearings on the Food and Drug Administration's (FDA) implementation of the statute in July 1982 (336) and issued an oversight report in 1983 (338). The General Accounting Office also reviewed implementation of the Medical Device Amendments and issued its report in September 1983 (331). Most recently, in February 1984, the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce held oversight hearings on the law and its implementation (337). These hearings and investigations have focused on FDA's priorities and pace in implementing the amendments and on those provisions of the law which, in view of the experiences gained since the law's enactment, have not worked as intended.

The 1976 law, its history, its implementation by FDA, and key unresolved issues are addressed in this chapter. The chapter concludes with a presentation of a range of options addressed to the major objectives of the law.

LEGISLATIVE HISTORY OF DEVICE REGULATION

Medical device regulation was first authorized in the Federal Food, Drug, and Cosmetic Act of 1938. (This act is best known for requiring premarket notification for the safety of new drugs, a requirement that was extended to include premarket approval of the efficacy as well as the safety of new drugs in the Drug Amendments of 1962.) The 1938 act defined medical devices as (21 U.S.C. § 321 (h)):

> . . . instruments, apparatus, and contrivances, including their components, parts and accessories, intended (1) for use in the diagnosis, care, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals.

The 1938 act authorized FDA to inspect any site in which devices were manufactured, processed, packed, or held (21 U.S.C. § 374). It also authorized FDA to seize adulterated or misbranded medical devices; request an injunction against their production, distribution, or use; or seek criminal prosecution of the responsible manufacturer or distributor. But the agency could not take action until after a device had been marketed.

In the early regulatory actions taken against adulterated or misbranded devices, FDA was able to use expert testimony to prove its allegations. Over time, however, FDA increasingly had to test devices suspected of violating the law in order to remove these devices from the market (340).

As medical devices became more complex after World War II, attention turned to the regulation of legitimate devices as well. But FDA could still act only *after* devices were distributed and also

had the burden of proving that a particular item was misbranded or unsafe, because devices were not subject ***to premarket*** approval (12). In the late 1960s, however, the courts ruled that certain products (such as nylon sutures and antibiotic-sensitive discs) that fell in the grey area between drugs and devices could legally be considered drugs and subjected to premarket approval requirements for new drugs (12,302); subsequently, FDA regulated as "new drugs" such products as some intrauterine devices (IUDs), some contact lenses, and some in vitro diagnostic products.

Furthermore, during the late 1960s, Congress addressed public health problems associated with radiation emissions from electronic products. Under the Radiation Control for Health and Safety Act of 1968 (Public Law 90-602), Congress established a radiation control program to authorize the establishment of standards for electronic products, including medical and dental radiology equipment.

From the early 1960s to 1975, six Presidential messages were given and 28 bills were introduced to enact medical device legislation.

A 1969 Department of Health, Education, and Welfare review of the scientific literature for injuries associated with medical devices that was conducted by the Cooper Committee (named after its chairman, Theodore Cooper, then Director of the National Heart, Lung, and Blood Institute of the National Institutes of Health) estimated that over a 10-year period, 10,000 injuries were associated with medical devices, of which 731 resulted in death (339).

The vast majority of these problems were associated with three device types: artificial heart valves, 512 deaths and 300 injuries; cardiac pacemakers, 89 deaths and 186 injuries; and intrauterine contraceptive devices, 10 deaths and 8,000 injuries (339). As observers noted, however, there had been no sensational event or public tragedy to spur more stringent regulation of medical devices such as the events leading to the 1962 Drug Amendments (165,328).

Additional examples of hazards associated with medical devices were documented in congressional hearings in 1973. These included prosthetic and orthopedic implants of improper materials, cardiac defibrillator with faulty electrical circuitry, incubators in which temperatures reached as high as 1450 F, plastic tracheotomy tubes with obstructions, and faulty valves on emergency oxygen respirators (339).

The developments just described eventually culminated in the enactment of the Medical Device Amendments of 1976 (Public Law 94-295).

THE MEDICAL DEVICE AMENDMENTS OF 1976

The situation prior to enactment of the Medical Device Amendments in 1976 was that FDA could impose premarket approval requirements on only a limited number of devices that could legally be considered new drugs (see above). FDA did have the power to inspect the premises where devices were manufactured and distributed, but had no power to require that owners of these premises notify FDA that they were in the device business. And FDA could attempt to remove mislabeled or unsafe devices only on a case-by-case basis after the devices had been marketed.

As a result of the 1976 Medical Device Amendments, FDA currently has the authority:

- to require that businesses involved with medical devices register their establishments and list their devices annually,
- to impose regulatory requirements (standards or premarket approval) in proportion to the degree of risk of a device, and
- to impose other general controls on all devices to assure safety and effectiveness.

FDA continues to have the authority granted by the 1938 act to inspect any establishment in which devices are manufactured, processed, or packed, whether or not these establishments are exempt from registration.

The definition of medical device was changed in the 1976 amendments to (Public Law 94-295):

> . . . an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part or accessory, which is—
> (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
> (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
> (3) 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 manor other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

This last clause in the definition (not achieving its principal purposes through "chemical action within or on the body" and "not dependent upon being metabolized") distinguishes devices from drugs.

Devices are to be categorized by type, on the basis of recommendations from FDA classification panels, into three regulatory classes reflecting their potential risk:

- Class I—general controls,
- Class II—performance standards, and
- Class III—premarket approval.

Class I, general controls, encompasses devices for which general controls authorized by the act are sufficient to provide reasonable assurances of safety and effectiveness. Tongue depressors are an example. Manufacturers of Class I and all other devices must register their establishments and list their devices with FDA, notify FDA at least 90 days before they intend to market the device, and conform to good manufacturing practices. Good manufacturing practices apply to the manufacturing, packing, storage, and installation of devices.

Class II, performance standards, contains devices for which general controls are considered insufficient to ensure safety and effectiveness and information exists to establish performance standards. X-ray devices are an example.

Class III, premarket approval, applies to devices for which general controls are insufficient to ensure safety and efficacy, information does not exist to establish a performance standard, and the device supports life, prevents health impairment, or presents a potentially unreasonable risk of illness or injury. Cardiac pacemakers are an example.

Preamendments devices were to be so classified and placed in Class I, II, or III. Postamendments devices found to be "*substantially equivalent*" to products on the market before 1976 were to be put into the same class as their preamendments counterparts and could be marketed immediately, although those in Class III could eventually be required to demonstrate safety and effectiveness. Other postamendments devices were to be automatically classified into Class 111, although the manufacturer could petition FDA for reclassification into Class I or II; thus, these devices could not be marketed until they had completed FDA premarket approval for safety and effectiveness,

In implementing the 1976 amendments, preamendments Class 111 devices and their postamendments substantially equivalent counterparts were to be treated differently from truly new postamendments Class III devices. The 1976 amendments stipulate that manufacturers of preamendments Class III devices cannot be required to present safety and effectiveness evidence until 30 months after the effective date of a final classification regulation or until 90 days after publication of a final regulation requiring submission of evidence on safety and effectiveness, whichever period *is* longer (21 U.S. C. § 351(f)(2)(B)). In the interim, preamendments Class 111 devices and their postamendments substantial equivalents can continue to be marketed, subject only to the same general controls as applied to Class I devices.

Manufacturers of any of the following devices are required by section 510(k) of the law to notify FDA at least 90 days prior to marketing them:

- a device that is to be marketed for the first time,
- a device or product line that may be similar to one already marketed by another manufacturer, or
- a version of an existing device in a form sig-

nificantly changed or sufficiently modified to affect its safety and effectiveness.

The manufacturer's 510k premarket notification must contain enough information so that FDA can determine whether or not the device is "substantially equivalent" to a device already being marketed. To be found substantially equivalent, a postamendments device need not be identical to a preamendments device, but must not differ markedly in materials, design, or energy source.

The legislative history reflects a congressional intent that the term "substantially equivalent" be construed narrowly where necessary to assure safety and effectiveness, but less narrowly in instances where differences between a postamendments device and a preamendments device did not relate to safety and effectiveness (340). If FDA determines that a postamendments device is substantially equivalent to one already in use, the manufacturer may market the device.

If FDA finds that a device is not substantially equivalent to one already in use before the 1976 amendments, the device must go through a premarket approval process. In this case, it is automatically classified into Class 111, although the manufacturer may petition FDA to reclassify it into Class I or Class II. (Class I devices can be marketed, subject only to the general controls summarized earlier. Since FDA has published no performance standards for Class II devices (see section on "Performance Standards" below), these devices have been subject only to general controls.) For a Class III device that is not substantially equivalent to a pre-1976 device, information must be provided to FDA to document its safety and effectiveness before the device can be approved by FDA for marketing.

In order to develop the safety and efficacy information necessary for market approval of a Class III device, the sponsor of such a device may apply to FDA for an "investigational device exemption" (IDE). An IDE, the parallel to the investigational new drug (IND) process in drug regulation, permits limited use of an unapproved device in controlled settings. Upon completion of clinical investigations under the IDE, the sponsor may submit to FDA a premarketing approval application (PMAA) presenting the results of the clinical investigations, an explanation of what the device consists of and how it works, manufacturing data that show compliance with good manufacturing practices, and other information that FDA may require.

If FDA approves this PMAA, the device may be marketed. (The amendments provide an alternative to the IDE/PMAA route to marketing approval for Class III devices, called a "product development protocol, " but this has never been used. The major difference between the product development protocol and the IDE/PMAA process is that in the former, FDA would participate in deciding how the device is to be tested. Once the product development protocol is completed, the testing results would be submitted to FDA for approval of the device for marketing (388).)

Finally, the situation for certain "transitional devices" (i.e., devices that were regulated as "new drugs" before enactment of the 1976 amendments) is comparable to that for postamendments devices that are not substantiality equivalent to preamendments devices. Transitional devices are automatically classified into Class 111, which requires premarket approval, but may be reclassified, subsequent to petitioning FDA, into Class I or Class II,

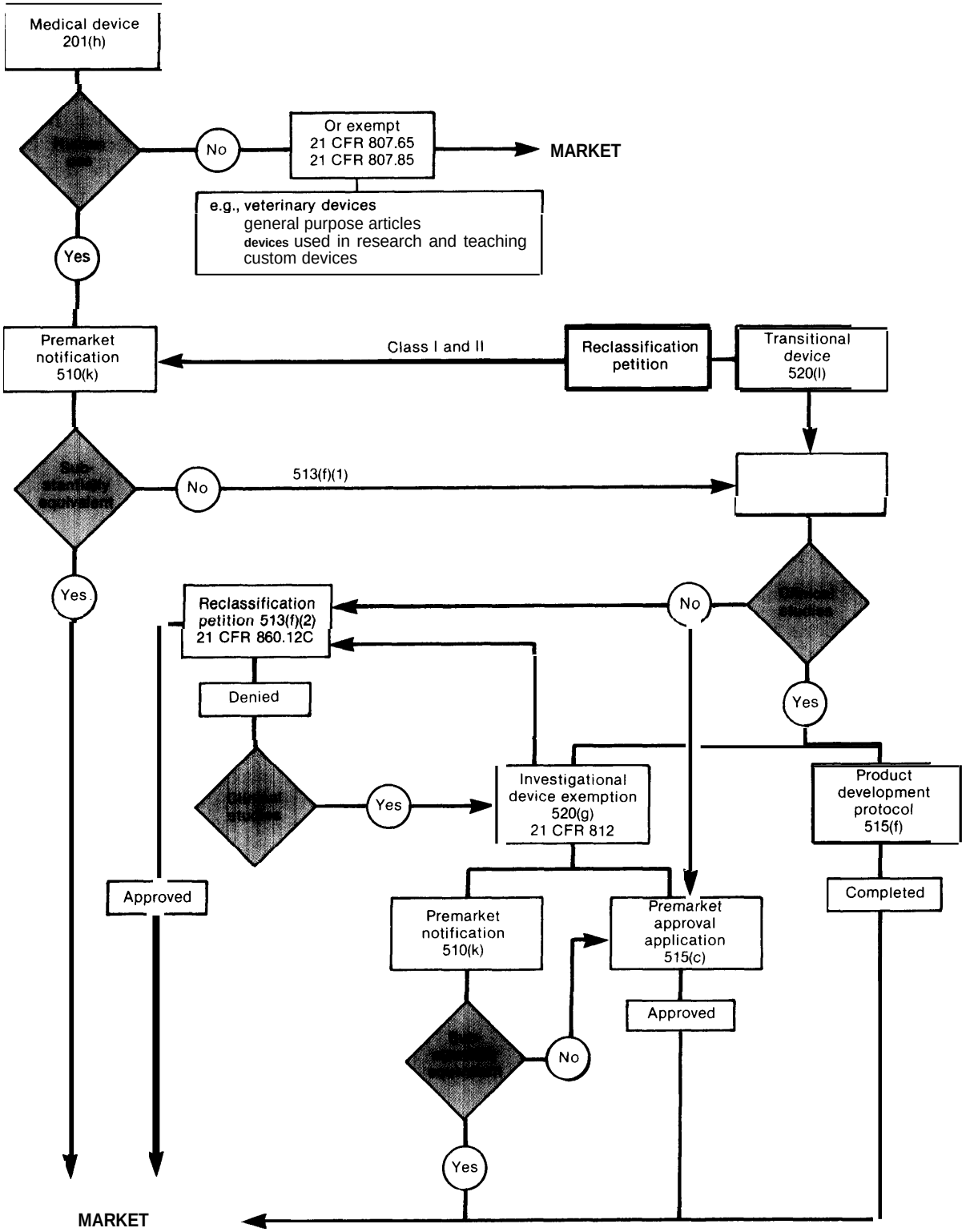
The current process of getting a medical device to market is summarized in figure 1.

The Medical Device Amendments contain other provisions worth noting that are applicable to all medical devices. First, sale, distribution, or use of a device may be restricted by FDA if there cannot otherwise be reasonable assurances of its safety and effectiveness. A device maybe banned if it presents substantial deception or an unreasonable and substantial risk of illness or injury.

Second, manufacturers, importers, and distributors of devices may be required to establish and maintain additional records, make reports, and provide information to FDA to assure that their devices are safe and effective.

Third, devices are subject to the color additive provisions of the Federal Food, Drug, and Cosmetic Act, but only if the color additive comes in direct contact with the body for a significant period of time.

Figure 1.—How To Get to Market With a Medical Device



SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration, Bureau of Medical Devices, *Regulatory Requirements for Marketing a Device* (Washington, DC: U.S. Government Printing Office, 19S2).

Fourth, because of concern over the impact of the 1976 amendments on small manufacturers, a provision of the law stated that an office should be established to provide technical assistance to small firms. FDA has therefore organized an Office of Small Manufacturers Assistance to help small firms with the regulatory requirements.

Finally, any medical device that can be marketed legally in the United States can be exported legally without further approval by the FDA. Medical devices that have not been approved for use in the United States may also be exported under certain conditions. *Prior FDA approval* is needed for export of devices that: 1) are in violation of performance standards, 2) are subject to premarket approval, 3) are subject to limited use under an IDE, or 4) are banned in the United States. These four types of devices can be exported only if they have the approval of the country to which the device is to be exported, and if FDA has determined that exportation of the device is not contrary to public health and safety (21 U.S.C. § 381(d)(2)). *&y* other type of device that cannot be marketed in the United States may be exported *without FDA* ***approval*** if the device: 1) meets the specifications of the foreign purchaser, 2) does not conflict with the laws of the country of the foreign purchaser, 3) is labeled for export, and 4) is not sold or offered for sale domestically (21 U.S.C. § 381(d)(l)). Although prior FDA approval is not required, FDA can at any time require the exporter of such a device to show that the aforementioned requirements are being met.

IMPLEMENTATION OF THE MEDICAL DEVICE LAW

Registration of Firms and Listing of Devices

Federal regulations require the following businesses involved with medical devices to register their establishments with FDA and list their devices annually (21 CFR pt. 807.20):

- manufacturers and other specified processors of devices,
- manufacturers of device components or accessories that are ready to be used for and labeled for a health-related purpose,
- initiators or developers of device specifications,
- repackagers and relabelers, and
- initial distributors of imported devices.

Manufacturers of device components and raw materials who would not otherwise be required to register, dispensers of devices, licensed medical practitioners, manufacturers of general-purpose articles, manufacturers of devices solely for veterinary use, and manufacturers of devices solely for research and training are exempt from registration (21 CFR pt. 807.65).

The number of device establishments registered with FDA in 1980 was 6,073. (This number differs from the number of establishments cited in ch. 2, mainly because the FDA list includes nonmanufacturing entities such as distributors.) By 1982, the number had increased to 7,636 registered establishments, 6,585 domestic and 1,051 foreign, listing approximately 41,500 products. More than 95 percent of the establishments had fewer than 500 employees, and more than half had fewer than 50 employees (143). Registration lists change significantly from year to year. In 1983, for example, 1,100 firms canceled their medical device status, while 1,800 firms registered for the first time with FDA (206).

Two studies by FDA's Office of Planning and Evaluation measured "baseline" conditions in order to track changes that may occur in the future. Some of the studies' principal findings on device establishments in 1980 were as follows (392):

- Eighty-two percent of registered domestic establishments manufactured devices, 20 percent imported devices, and 22 percent repackaged devices (device establishments may have more than one function).
- Sixty-nine percent of domestic establishments were the sole site operated by the owner/operator, while 28 percent were subsidiaries, branches, or divisions.

- Ninety-three percent of domestic owner/operators (3,948 out of 4,245 in 1980) operated only one medical device establishment.
- Forty-two percent of the domestic establishments had 20 or fewer employees, while 29 percent had 100 or more employees.
- Larger establishments were more likely than small establishments to: 1) produce more types of devices, 2) make an "exclusive" device (a device made by only one or two establishments), 3) make a Class III device, or 4) make a "critical" device (defined below in the section on "Good Manufacturing Practices").
- Sixty-four percent of listed manufacturers made devices in only one medical specialty area (as defined by FDA's list of classification panels).
- Medical device establishments other than those making diagnostic devices averaged 4.4 products each, while diagnostic device establishments averaged 6.4 products each.
- There was little overlap between manufacturers of medical devices and diagnostic devices. Establishments making dental, ophthalmic, and radiological devices were also highly specialized. Therefore, there appears to be a segmentation of the industry between medical and diagnostic devices, and a further segmentation of the medical devices portion of the industry between establishments that are highly specialized and those that make devices in several areas.

The other study (391) looked at "availability" of devices, or the number of products for each device type. A device type may include all products of a particular type (e.g., cardiac pacemakers) or may include groupings of separate types of devices that are similar. The more products of a type, the greater the availability of products of that type. The analysis in this study was based on device classifications that were established enough to use at the time of the analysis, or devices from about half of the FDA classification panels established (see "Classification" section below). Its principal findings on availability were as follows (391):

- On average, there were nine products per type, i.e., each device type was made by an average of nine establishments.
- Product availability was related to class of device. Class I device types averaged 13.1 products per type; Class II, 7.9 products; and Class III, 4.5 products.
- Devices with only one or two manufacturers comprised 28 percent of all device types. Forty-one percent of Class 111, 28 percent of Class II, and 24 percent of Class I device types had only one or two manufacturers.
- Foreign establishments made 17 percent of the products examined. Eleven percent of all exclusive types had only foreign manufacturers; 4 percent were made solely by foreign manufacturers.
- Foreign products accounted for 21 percent of Class III devices, 19 percent of Class II, and 15 percent of Class I devices.
- More than one-third of all obstetrics-gynecology products and nearly two-thirds of Class I neurological products were of foreign origin.

Premarket Notification

In addition to listing their devices annually, device establishments must notify FDA through the 510k notification process (see above) when they intend to market new devices.

Postamendments devices that are not found by FDA to be "substantially equivalent" to preamendments devices or to postamendments devices that have been reclassified into Class I or II are presumed to be Class III, and hence to need premarket approval unless the device's sponsor successfully petitions FDA to reclassify the device into Class I or II. However, the overwhelming majority of postamendments devices are from manufacturers who are marketing existing device types for the first time or who have devices that are minor modifications of existing devices. Thus, the 510k premarket notification process, together with the FDA finding that devices are substantially equivalent to preamendments devices, has become the predominant route by which postamendments devices have reached the market.

An indication of the extent to which postamendments devices have been regulated through the 510)k notification process is reflected in the fact that, of more than 17,000 notifications received for fiscal year 1977 through fiscal year 1981, only

approximately 300 were found to be not substantially equivalent and therefore automatically placed in Class III. For 65 of these, petitions for reclassification were received; 28 were approved, 5 denied, 28 withdrawn or converted to other types of submissions, and 4 were still active at the end of fiscal year 1981, Of the 28 approvals, 3 were reclassified from Class III to I, and 25 from Class III to II (143). The number of 510k submissions and the number of submissions found not substantially equivalent since 1976 are summarized by year in table 32.

The purpose of the 510k notification process was to keep FDA apprised of what was going on in the industry. The concept of "substantial equivalence" was included in the law to address the question of how to treat pre- and postamendments devices fairly. Two issues were involved: 1) a double standard would exist if a postamendments device had to go through the premarketing approval process before it could be marketed, while an identical preamendments device would continue to be marketed; and 2) a type of monopoly would in effect be given to a preamendments device if identical pre- and postamendments devices were treated differently.

The 510k process, together with a determination of substantial equivalence, has been used extensively for postamendments devices to avoid Class III designation and its automatic requirement for premarket approval, or to avoid the involved rulemaking process necessary to reclassify such devices from Class III to Class I or II.

Use of the substantial equivalence clause to permit the marketing of devices without premarket approval has been encouraged by FDA's regulations and practices. First, FDA's initial proposed regulations that would have required submission of a 510k notice if modifications could affect safety and effectiveness were changed. In the proposed regulations, if FDA determined that modifications could affect safety and effectiveness, there would be no finding of substantial equivalence, and an evaluation of the difference would have been made in a PMAA or in a reclassification petition from automatic Class III designation (53). In the final regulation, however, FDA changed the wording to "changes that could *significantly* affect the safety or effectiveness of the device" (emphasis added) (21 CFR pt. 807.81(a)(3)(i)).

Second, FDA allows manufacturers to trace back through a chain of substantially equivalent postamendments devices to a device on the market before the amendments were enacted. For example, a 1982 device may be approved as substantially equivalent to a 1981 device, which was approved as equivalent to a 1979 device, and so on eventually back to a preamendments device. This practice has been labeled "piggybacking" or, alternatively, "equivalence creep" (53,331).

Third, the amount of data required to show substantial equivalence varies widely, depending on the device. All devices that have been determined not to be substantially equivalent and which thus must go through premarket approval are reviewed centrally, but there is no such central review for devices that have been found to be substantially equivalent (47).

Another issue relating to the 510k notification process is whether or not notification requirements should be applied to Class I devices. In September 1982, the Scientific Apparatus Makers Association petitioned FDA to drop 510k notification requirements for Class I device types and to simplify reporting requirements for Class 11 and III (82). The petition claimed that Class I devices would still be subject to the registration require-

Table 32.—Number of "510k" Submissions and Number Found Not Substantially Equivalent, 1976-83

Year	Number of "510k" submissions	Number found not substantially equivalent
1976 (7 months)	1,362	*8*
1977	2,427	*47*
1978	2,180	*43*
1979	2,714	*44*
1980	3,316	*73*
1981	3,652	*63*
1982	3,780[a]	*55*
1983	NA[b]	3 2[d]
Total	19,431C	365[d]

[a]Estimate.
bNA indicates information not available.
[c]Excluding 1983.
'As Of July 1983.

SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration, unpublished data, Silver Spring, MD, 1983.

ments and to surveillance under the good manufacturing practices regulations.

Furthermore, notification of intent to market Class II devices for which no standards exist could be simplified, and additional information could be required only for Class III devices and for Class 11 devices that have performance standards. The petition claimed that these changes would still provide reasonable assurances against new devices being marketed without a change in classification or without premarket approval.

FDA subsequently denied the petition, telling the Scientific Apparatus Makers Association that the legislative intent was to make decisions on the basis of generic types of devices, not whether or not devices were in Class I (80). In addition, FDA was already exempting some device types from 510k notification requirements. For example, in its final rule on classifying General Hospital and Personal Use devices, FDA exempted 30 generic types of Class I devices from notification requirements. They included medical absorbent fibers and specimen containers, if the devices are not labeled or otherwise represented as sterile (306).

Classification of Devices

By the beginning of 1984, FDA had completed classification of preamendments device types in only 11 of its 19 medical specialty sections and had issued proposed classifications for the other 8 sections (see table 33). Final and proposed classifications as of February had placed 460 device types in Class I, 1,086 in Class II, 138 in Class III, and, depending on the particular product or use of the product of a specified device type, 27 in Class I or II, 13 in Class II or III, and one in Class I, II, or 111 (see table 34).

A "device type" may include all products of a particular type (see discussion of availability in the section above, "Registration of Firms and Listing of Devices") or may include groupings of separate types of devices that are similar. Thus, for example, the device type "obstetrics-gynecology specialized manual instruments" was formed by merging 18 separate instruments such as umbilical clamps, gynecological surgical forceps, and uterine sounds (391).

Documentation of safety and effectiveness for preamendments Class III devices was not immediately required but eventually has to be submitted for marketing to continue. As previously explained, the 1976 amendments provided a grace period of 30 months before such requirements could be imposed, but the grace period does not begin until final classification is made. Therefore, for example, the earliest date that FDA could call for evidence of safety and effectiveness of Class III devices in the eight medical specialty sections for which final classifications had not been made at the beginning of 1984, even if they were finally classified early in the year, would be in 1986. For the 11 medical specialties with final classifications, the grace period had ended for 6 by 1984 (see table 34).

Tables 33 and 34 show the number of Class III device types for which the 30-month grace period applies. An indication of the number of device *products* that are involved can be gleaned from the number of postamendments Class III devices found to be substantially equivalent to preamendments Class III devices. The number of such products is summarized in table 35 by medical specialty and year of notification. From the table, it can be seen that, in addition to Class III products on the market prior to the 1976 amendments, there were over 1,000 postamendments Class 111 products in use by 1983 through a finding of substantial equivalence. Nearly two-thirds of these products were cardiovascular devices.

On May 5, 1982, the Health Research Group petitioned FDA to issue regulations requiring device manufacturers to submit PMAAs for preamendments Class III neurological devices (252). These devices had been classified in final regulations effective October 4, 1979, and the Health Research Group had petitioned FDA shortly after the 30-month grace period had ended. FDA's response was that the 30-month time period established only the *earliest* date FDA could act (85).

The Health Research Group subsequently wrote to Rep. John Dingell (D-Mich.), Chair of the House Committee on Energy and Commerce and also Chair of its Subcommittee on Oversight and Investigations, asking that oversight hearings be held and that there be consideration of an amend-

Table 33.-Classification of Preamendments Device Types by Medical Specialty Category, February 1984

Medical specialty category	Proposed	Final	Class I	II	III	I or II	II or III	I, II, or III	Total
Neurology	11128/78	9/4/79	24	66	11	0	0	0	101
Cardiovascular	4/9/79	2/5/80	3	108	24	1	2	0	138
Obstetrics-gynecology	4/3/79	2/26180	5	48	16	0	0	0	69
Hematology	9/11/79	9/12/80							
(combined)			42	60	6	0	1	0	109
Pathology }	9/11/79	9/12/80							
General hospital and personal use	8/24179	10/21/80	51	39	2	2	0	0	94
Anesthesiology	11/2/79	7/16/82	21	105	7	0	1	0	134
Immunology	4122/80	1119/82							
} (combined)			93	64	5	0	0	0	162
Microbiology }	4122/80	1119182							
Physical medicine	8128/79	11123183	32	42	2	0	5	0	81
Gastroenterology-urology	1/23/81	11123183	9	32	9	4	2	0	56
Subtotal			280	564	82	7	1 1	0	**944**
Dental	12/30/80	—	49	122	13	1	0	0	**185**
General and plastic surgery	1/19182	—	23	25	5	0	1	0	**54**
Ear, nose, and throat	1122/82	—	10	47	10	0	0	0	**67**
Ophthalmology	1126/82	—	45	51	4	19	0	0	**119**
Radiology	1129182	—	7	64	0	0	1	1	**73**
Clinical chemistry	2112/82	—							
(combined)			31	175	0	0	0	0	206
Clinical toxicology }	2/12/82	—							
Orthopedics	712182	—	15	38	24	0	0	0	77
Subtotal			180	522	5 6	2 0	2	1	781
Total			**460**	1,086	138	27	1 3	1	1,725

SOURCE: *Federal* Register publications of specified dates

Table 34.—Classification Status of Preamendments Device Types, February 1984

Status	Class I	II	III	I or II	II or III	I II, or III	Total
Final	280	5 6 4	8 2 7	1 1	0	9 4 4	
Proposed	180	522	56	20	2	1	781
Total	460	1,086	138	27	13	1	1,725

SOURCE: See table 33.

ment to the device amendments that would clearly establish a definite time for submission of data for preamendments and substantially equivalent Class III devices (83). The Health Research Group petitioned FDA again in March 1983, this time for preamendments Class III obstetrics-gynecology devices and their substantial equivalents, pointing out that the 30-month grace period had ended on August 31, 1982 (253).

In September 1983, FDA issued its first ''Notice of Intent" to initiate proceedings requiring approval for continued marketing of preamendments Class III devices and their postamendments substantial equivalents in the five medical specialty categories for which the 30-month grace period had expired. FDA identified the following devices in these five medical specialty categories as being the first device types for which safety and effectiveness evidence would be required (321).

- Hematology and Pathology (combined)
  1. Automated differential cell counter
  2. Automated heparin analyzer
  3. Automated blood cell separator
- Cardiovascular
  1. Implantable pacemaker pulse
  2. Pacemaker programmer
  3. Replacement heart valve
- General hospital and personal use
  1. Infant radiant warmer
- Neurology
  1. Implanted cerebella stimulator
  2. Implanted diaphragmatic/phrenic nerve stimulator
  3. Implanted intracerebral/subcortical stimulator for pain relief

Table 35.—Number of Postamendments Class III Devices Found Substantially Equivalent to Preamendments Devices by Medical Specialty Category, 1976-83

Medical specialty category	1976 (7 mos.)	1977	1978	1979	1980	1981	1982	(as of 7/83)	Total
Anesthesiology [a]	1	3	5	3	9	3	1	2	27
Cardiovascular	33	71	89	121	114	143	94	51	716
Clinical chemistry	0	0	0	0	1	2	0	0	3
Clinical toxicology	0	0	0	0	0	1	0	0	1
Dental	2	6	5	5	4	6	11	3	42
Ear, nose, and throat	o	3	3	6	5	0	3	0	20
Gastroenterology-urology [a]	0	4	2	3	8	5	8	10	40
General and plastic surgery	6	5	2	6	5	14	2	5	45
General hospital and personal use [a]	0	1	0	2	2	2	2	1	10
Hematology [a]	o	9	2	8	4	0	3	1	27
Immunology [a]	1	4	1		3	3	2	1	16
Microbiology [a]	o	5	4	8	12	10	3	1	43
Neurology [a]	5	6	2	3	8	5	2	0	31
Pathology [a]	o	0	0	0	0	0	2	0	2
Obstetrics-gynecology [a]	2	2	3	1	3	2	0	2	15
Ophthalmology	2	3	7	5	3	3	9	6	38
Orthopedics	o	1	0	1	2	2	0	2	8
Physical medicine [a]	o	1	1	1	0	0	0	0	3
Radiology	o	0	0	1	0	1	3	0	5
Total	52	124	126	175	183	202	145	85	1,092

[a] Classification completed (as of the endof19S3) (see table 33).

SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration, unpublished data, Silver Spring, MD, 19S3.

- Obstetrics-gynecology
  1. Transabdominal amnioscope (fetoscope) and accessories
  2. Contraceptive uterine device (IUD) and introducer
  3. Contraceptive tubal occlusion device (TOD) and introducer

The Federal Register notice also announced that FDA was proposing a rule to require the filing of a PMAA for one of these devices, the implanted cerebellar stimulator. Four months after the announcement, no PMAAs had been submitted, probably because of difficulty in providing data that supported the stimulator's safety and effectiveness (86). If IDEs are obtained, however, the implanted cerebellar stimulator may continue to be used for the limited purpose of obtaining safety and effectiveness data from clinical trials (321).

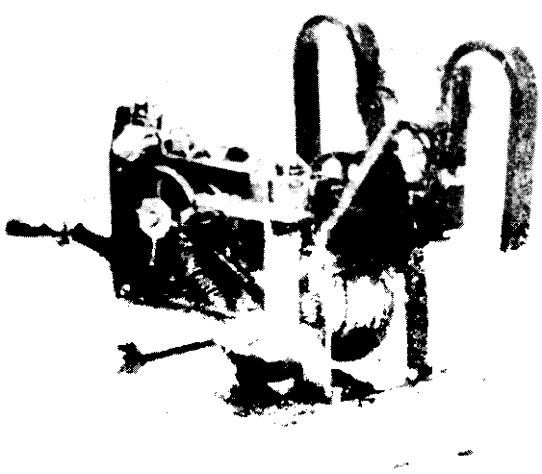
Reclassification of Devices

As explained earlier, the sponsors of postamendmerits devices that are not substantially equivalent to preamendments devices and are automatically put in Class III may petition FDA for reclassification into Class I or II. The major reclassification issue has not been with these devices, however, but with one of the transitional devices—contact lenses,

Under the 1976 Medical Device Amendments, transitional devices (products that had previously been regulated as ''newdrugs") were automatically classified in Class III and made subject to premarket approval requirements, although the manufacturers could petition FDA for reclassification. All contact lenses made of polymers other than polymethyl-methacrylate (hard lenses) had been previously declared to be "new drugs" and placed in Class 111 when the 1976 amendments were enacted. Subsequently, some manufacturers did the testing required to meet the premarket approval requirements.

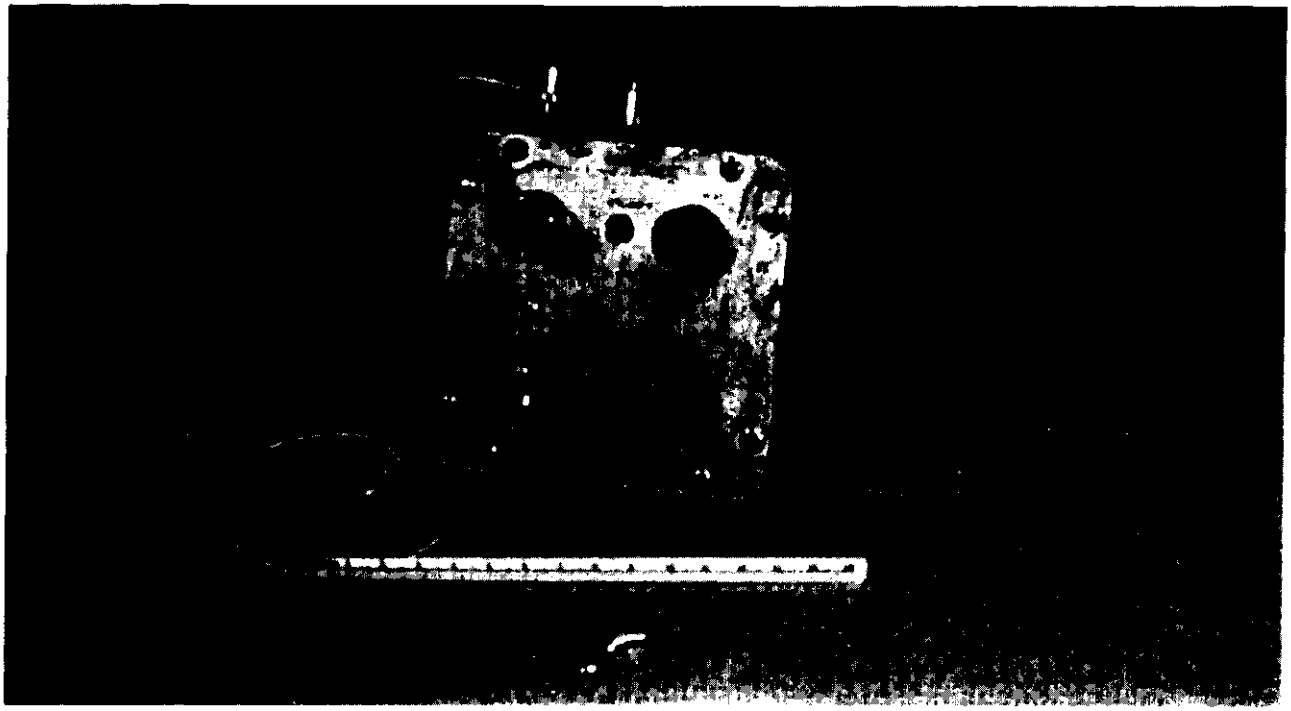
In March 1981, the Contact Lens Manufacturers Association (CLMA), representing predominantly small contact lens manufacturers, petitioned FDA to reclassify from Class 111 to 11 contact lenses consisting principally of rigid plastic materials. CLMA's contention was that these lenses were safe and effective enough to be placed in Class II, thus making further testing unnecessary.

FDA subsequently concluded that CLMA's petition did not meet all of the requirements of the regulations (21 CFR pt. 860.123). The agency also



1932

Early 1950s



Mid 1970s

Photo credits: Alan R. Kahn

This picture shows three steps in the evolution of the cardiac pacemaker, from a device carried on the patient's back, to an external device with internal leads, to a fully implantable pacemaker Implantable cardiac pacemakers are regulated as Class Ill devices

determined that the objective of CLMA's petition was meritorious, however, and in November 1982, proposed to reclassify both daily-wear soft contact lenses and daily-wear rigid gas-permeable contact lenses from Class III to Class I (rather than to Class II) (313).

In December 1983, FDA withdrew the proposed rule on rigid gas-permeable lenses on the basis of the fact that its review found insufficient publicly available, valid scientific evidence to show that the device was safe and effective (323). The information had to be based on "valid scientific

evidence" (21 CFR pt. 860.7(c)), and that evidence had to be publicly available because the 1976 amendments prohibit the use of trade secrets, confidential commercial information, or detailed information on safety and effectiveness contained in the premarket approval application of manufacturers who have succeeded in obtaining approval for their devices.

Following its decision not to down-classify rigid gas-permeable contact lenses, however, FDA decided to review its contact lens guidelines for IDEs and PMAAs to determine under what conditions some parts of the guidelines could be avoided, thereby simplifying the premarket approval process (207).

Good Manufacturing Practices

Good manufacturing practices regulations, which apply to the manufacturing, packing, storage, and installation of devices, are one of the important ways in which Class I devices were to be regulated. They also apply to Class II and III devices.

The good manufacturing practices regulations implemented by FDA for device manufacturers distinguish between "critical" and "noncritical" devices (21 CFR pt. 820):

> "Critical device" means a device that is intended for surgical implant into the body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user.
>
> "Noncritical device" means any finished device other than a critical device.

Most critical devices are in Class III, but not all Class III devices are critical.

The good manufacturing practices regulations require that the manufacturer keep a device master record containing the device's specifications, production processes, and quality assurance procedures; a historical record of the device indicating control numbers and dates of manufacture and distribution; and complaint files regarding the device's performance. For critical devices, the manufacturer must have more detailed monitoring of production and distribution and must maintain individual control numbers and device master records. Additional compliance programs are cited specifically for manufacturers of cardiac pacemakers and sterile devices (389). FDA has exempted manufacturers of some noncritical devices in Class I (e.g., specimen containers) from most of the record-keeping requirements of the good manufacturing practices regulations.

In a review of reports of good manufacturing practice inspections conducted primarily on Class 11 and III device manufacturers from January 1979 through December 1981, out of 3,811 good manufacturing practices inspections, 62 regulatory actions were taken. FDA concluded that the compliance rate for larger firms tended to be somewhat better than for smaller firms, but overall compliance by the industry was good, and there was a reasonable level of compliance for smaller firms (143).

Performance Standards

Proposed and final classifications as of early 1984 had placed nearly 1,100 of the more than 1,700 device types in Class 11 (see tables 33 and 34, above). Yet no mandatory performance standards have been issued by FDA for any Class II device types.

Class 11 has become a de facto catchall regulatory category, intermediate between the minimum regulatory requirements imposed by Class I general controls and the full premarket approval process associated with Class 111 devices. Operationally, however, because no performance standards have been issued for Class II device types, Class II devices have been regulated as though they were Class I devices.

FDA has approached further regulation of Class II device types in several ways. First, in 1982, FDA proposed that the following steps could be considered before promulgation of a mandatory performance standard (387):

- request that manufacturers voluntarily solve device problems,
- publicize particular device problems,
- publish educational and technical information directed at device use,
- participate in developing a voluntary standard,

- make use of other general controls such as those for adulteration and misbranding, and
- develop guidelines.

Second, in mid-1982, the Administration submitted to Congress a proposal to repeal the present statutory procedures for developing and establishing performance standards for medical devices by substituting a simpler notice-and-comment rulemaking procedure under the Administrative Procedures Act. The device amendments require a five-step process: 1) initiate by *Federal Register* notice a proceeding for a performance standard, which provides the opportunity for manufacturers to request a change in classification, denial of requests for reclassification, or initiation of reclassification by ***Federal*** *Register* notice; 2) invite persons by ***Federal*** *Register* notice to submit an existing standard as a proposed performance standard or an offer to develop such a standard; 3) accept or reject such offers or proceed to develop such standards; 4) publish a notice of proposed rulemaking; and 5) promulgate a performance standard (21 CFR pt. 861.20).

The proposal the Administration submitted to Congress would have eliminated the second and third steps. Rep. Henry A. Waxman (D-Calif.), Chair of the Subcommittee on Health and the Environment of the House Committee on Energy and Commerce, agreed to sponsor the bill but added a section requiring manufacturers to notify FDA if they learn of device defects that present unreasonable risks of substantial harm (see subsequent section on "Postmarketing Surveillance" for a related discussion). H.R. 7052, the Medical Device Amendments of 1982, was introduced by Rep. Waxman on August 19, 1982, but was not acted on. Similar legislation, including discretionary authority to apply performance standards, was reported to be under consideration at the Department of Health and Human Services/FDA at the beginning of 1984 (87).

Third, in mid-1983, FDA finally identified 11 priority Class II devices, announced its intent to proceed with development of performance standards, and started the five-step process (see above) by providing the opportunity to submit a request for a change in the classification of the first of these 11 devices, the continuous ventilator (320).

Do the 1976 Medical Device Amendments in fact *require* the use of performance standards? Two sections of the amendments seem in conflict on this point. Section 514(a)(l) of the act states that: "The Secretary ***may*** by regulation . . . establish a performance standard for a Class II device" (emphasis added). But the act's definition of a Class 11 device is: "A device which cannot be classified as a Class I device because the [Class I] controls . . . by themselves are insufficient to provide reasonable assurance of the safety and effectiveness of the device, *for which there is sufficient information to establish a performance standard* to provide such assurance, and for which *it is therefore necessary to establish for the device a performance standard* . . . to provide reasonable assurance of its safety and effectiveness" (emphasis added) (§ 513(a)(l)(B)).

What if there is *insufficient* information to establish a performance standard? That condition in itself does not require Class III designation. A device is a Class III device if it "cannot be classified as a Class II device because insufficient information exists for the establishment of a performance standard . . . *and* (it) is purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or presents a potential unreasonable risk of illness or injury" (emphasis added) (§ 513(a)(l)(0). FDA, in classifying a device into Class II, has had to conclude that sufficient information to develop performance standards in fact exists (see the definition of Class II, above). Yet the fact that no mandatory performance standards have been issued casts doubt on this conclusion.

Moreover, FDA has chosen Class II instead of Class III designation even in some cases where a device was of an implantable type. This is illustrated by proposed classifications for General and Plastic Surgery devices, where seven implantable device types (including artificial chins, ears, and noses) were proposed for Class II instead of Class 111 designation (311). The Health Research Group, commenting on these proposed classifications, stated that implantable devices should be in Class III (253).

Investigational Device Exemptions

An IDE permits limited use of an unapproved Class III medical device in controlled settings for the purpose of collecting data on safety and effectiveness. This information can subsequently be used in support of a PMAA.

The regulations that FDA has implemented on IDEs make a distinction, which is not expressly stated in the law, between "significant risk" and "nonsignificant risk" devices. A "significant risk device" is an investigational device that (21 CFR pt. 812.3(m)):

(1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
(2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
(3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
(4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Sponsors of investigations of significant risk devices must obtain approval by an institutional review board, if one exists, and must also apply for an IDE from FDA. Investigations may not begin until FDA approval is granted. The determination of whether a device is a significant risk device is initially made by the sponsor. The institutional review board reviewing the investigational plan also makes this determination and has the authority to approve, require modifications, or disapprove the investigational plan. If the review board disagrees with a sponsor's conclusion that a device is a nonsignificant risk device, the sponsor has to notify FDA and apply for an IDE.

If no institutional review board exists or if FDA finds the institutional review board's review inadequate, the sponsor may submit an application for an IDE directly to FDA (21 CFR pt. 812.62). FDA will then decide whether an IDE is needed. The sponsor of a nonsignificant risk device need not apply for an IDE but must obtain approval to test the device from the institutional review board of the institution where testing will occur and must meet certain reporting, recordkeeping, and monitoring requirements.

The IDE not only allows device sponsors to test the Class III device before approval is obtained for marketing, but also is a method of keeping FDA apprised of the existence of clinical testing. For nonsignificant risk devices, FDA need not actually be informed of the specifics of testing, and these devices are considered to have approved applications for IDEs as long as the institutional review board has approved the testing and certain recordkeeping and other requirements are met (21 CFR pt. 812.2(b)).

(At a December 1983 meeting of the Food and Drug Law Institute, an FDA official unofficially raised the idea of a written notification to FDA of the existence of a nonsignificant risk investigation in addition to the normal nonsignificant risk IDE procedures. The principal purpose was to inform FDA of the existence of clinical testing to ensure that a reasonable amount of safety and effectiveness information was gathered in preparation for premarket approval, and to prevent manufacturers from profiting on unapproved devices (81).)

In a few instances, FDA guidelines have established requirements concerning the numbers of patients required in a clinical study and the length of time they need to be followed. For example, in December 1983 FDA advised manufacturers of YAG (yttrium aluminum garnet) lasers, a Class 111 device which is used in cataract surgery, that a reasonable study population was 500 patients studied for 6 months and that the sponsors should not add to the study without FDA approval (81).

The number of significant risk IDEs that have been issued from 1977 to 1982 is summarized in table 36 by medical specialty category. The numbers in that table reflect the changing status of the IDE regulations. Until 1978, FDA required IDE applications solely for studies of certain Class III devices that had been previously regulated as new drugs (i.e., "transitional devices"). In February 1978, the IDE regulations for intraocular lenses became effective (21 CFR pt. 813), and IDE ap-

Table 36.—Investigational Device Exemptions (IDEs) for Significant Risk Devices by Medical Specialty Category, 1977-82

Medical specialty category	1977	1978[a]	1979	1980[b]	1981	1982	Total
Anesthesiology	0	0	0	0	8	11	19
Cardiovascular	0	3	2	21	39	32	97
Clinical chemistry	0	0	2	0	0	1	3
Clinical toxicology	0	0	0	0	0	0	0
Dental	0	0	1	4	0	2	7
Ear, nose, and throat	0	0	0	1	1	4	6
Gastroenterology-urology	0	0	1	10	28	21	60
General and plastic surgery	4	1	2	5	7	12	31
General hospital and personal use	2	0	0	4	4	4	14
Hematology	0	0	0	0	0	0	0
Immunology	0	1	0	2	2	0	5
Microbiology	0	0	0	1	0	0	1
Neurology	0	0	3	2	4	9	18
Pathology	0	0	0	0	0	0	0
Obstetrics-gynecology	0	0	0	21	53	34	108[c]
Ophthalmology		48	21	24	34	34	162
Orthopedics	0	0	0	4	12	11	27
Physical medicine	0	0	1	0	2	0	3
Radiology	0	0	0	6	9	1	16
Total	7	53	33	105	203	176	577

[a]Intraocular lens regulation final in February 1978
[b]IDE regulation final in January 1980.
[c]Almost exclusively cervical cap studies.

SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration unpublished data, Silver Spring, MD, 1983

placations for intraocular lenses began to be received. In January 1980, IDE regulations applicable to other types of devices were made final (21 CFR pt. 812).

The relationship between requests for approval and FDA's finding that IDEs were in fact needed is indicated by the fact that nearly 60 percent of approximately 400 requests for approval of IDEs for significant risk devices that FDA received between July 1981 and July 1982 were approved with or without additional conditions within 30 days. The remainder were disapproved, subject toadditional justification, withdrawn by the sponsor, or returned to the sponsor with the finding that an IDE was not necessary (143).

Premarket Approval

In 1980, FDA developed guidelines for the submission of PMAAs and also published proposed regulations on premarket approval requirements (308). However, the regulations had not been finalized by early 1984. Under the guidelines currently inuse, when a PMAA is approved, the approval letter states that information on adverse reactions and device defects must be reported within 10 days. And according to an FDA prescription device regulation (21 CFR pt. 801.109) predating the 1976 amendments, certain devices may be sold or distributed only by or on the order of licensed practitioners. FDA has used these restrictions as a condition of approval for certain devices.

As indicated earlier, the only types of devices that have had to go through the full premarket approval process so far are: 1) postamendments devices that are not substantially equivalent to preamendments devices, and 2) ''transitional devices" that have not been reclassified as Class I or II and postamendments devices substantially equivalent to them. Preamendments Class III devices and their postamendments equivalents will eventually have to go through a similar approval process. In September 1983, FDA identified the first 13 preamendments Class III device types for which evidence of safety and effectiveness will soon be required if continued marketing is to be allowed (see section on "Classification of Devices, " above) (321).

The number of postamendments Class III devices that have successfully passed through the full premarket approval process and the number of transitional devices that have received premarket approval from 1977 to 1982 are summarized in table 37 by medical specialty category.

Table 37.—Approved Premarket Approval Applications (PMAAs) by Medical Specialty Category, 1977-82

Medical specialty category	1977	1978	1979	1980	1981	1982	Total
Approved PMAAs:							
Anesthesiology	0	0	0	1	3	4	8
Cardiovascular	1	0	4	2	3	5	15
Clinical chemistry	0	0	0	0	1	0	1
Clinical toxicology	0	0	0	0	0	0	0
Dental	0	0	1	0	1	0	2
Ear, nose, and throat	0	0	0	0	0	0	0
Gastroenterology–urology	0	0	1	0	0	2	3
General and plastic surgery	0	0	0	4	4	2	10
General hospital and personal use	0	0	0	1	2	2	5
Hematology	0	0	0	0	0	0	0
Immunology	0	0	0	3	0	0	3
Microbiology	0	0	5	4	2	1	12
Neurology	0	0	0	0	1	2	3
Pathology	0	0	0	0	0	0	0
Obstetrics-gynecology	0	0	0	0	0	0	0
Ophthalmology	0	0	6	12	22	20	60
Orthopedics	0	0	2	1	1	2	6
Physical medicine	0	0	0	0	0	0	0
Radiology	0	0	0	0	0	0	0
Total	7	0	19	28	40	40	128
Approved PMAAs for new devices:							
Anesthesiology	0	0	0	1	3	4	8
Cardiovascular	1	0	3	2	2	5	13
Clinical chemistry	0	0	0	0	1	0	1
Clinical toxicology	0	0	0	0	0	0	0
Dental	0	0	1	0	0	0	1
Ear, nose, and throat	0	0	0	0	0	0	0
Gastroenterology-urology	0	0	1	0	0	2	3
General and plastic surgery	0	0	0	0	2	1	3
General hospital and personal use	0	0	0	1	2	2	5
Hematology	0	0	0	0	0	0	0
Immunology	0	0	0	0	0	0	0
Microbiology	0	0	5	4	2	1	12
Neurology	0	0	0	0	1	2	3
Pathology	0	0	0	0	0	0	0
Obstetrics-gynecology	0	0	0	0	0	0	0
Ophthalmology	0	0	0	0	0	0	0
Orthopedics	0	0	2	1	0	1	
Physical medicine	0	0	0	0	0	0	4
Radiology	0	0	0	0	0	0	0
Total	7	0	12	9	13	18	53
Approved PMAAs for transitional devices:							
Anesthesiology	0	0	0	0	0	0	0
Cardiovascular	0	0	1	0	1	0	2
Clinical chemistry	0	0	0	0	0	0	0
Clinical toxicology	0	0	0	0	0	0	0
Dental	0	0	0	0		0	1
Ear, nose, and throat	0	0	0	0	0	0	0
Gastroenterology-urology	0	0	0	0	0	0	0
General and plastic surgery	0	0	0	4	2	1	7
General hospital and personal use	0	0	0	0	0	0	0
Hematology	0	0	0	0	0	0	0
Immunology	0	0	0	3	0	0	3
Microbiology	0	0	0	0	0	0	0
Neurology .....,	0	0	0	0	0	0	0
Pathology	0	0	0	0	0	0	0
Obstetrics-gynecology	0	0	0	0	0	0	0

Table 37.—continued

Medical specialty category	1977	1978	1979	1980	1981	1982	Total
Ophthalmology	0	0	6	12	22	20	60
Orthopedics	0	0	0	0			2
Physical medicine	0	0	0	0	1	1	2
Radiology	0	0	0	0	0	0	0
Total	0	0	7	19	27	22	75

SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration, unpublished data, Silver Spring, MD. 1983.

Approved transitional devices are heavily skewed toward ophthalmic products, which are almost exclusively contact lenses and contact lens cleaning solutions and, beginning in December 1981, intraocular lenses. Other examples of transitional devices include cardiovascular grafts, bone cement, absorbable sutures, and specific types of immunological tests.

"New" postamendments devices are also concentrated in a few medical specialties, but not to the extent that ophthalmic devices have dominated approved transitional devices. Among these new devices are cardiac valves, heart pacemakers and accessories, cardiovascular catheters, life-support monitoring systems, implantable infusion pumps, artificial hips, and antibody tests for infectious agents.

From 1977 through the end of 1982, 128 Class III products (53 "new" devices and 75 "transitional" devices) had gained premarket approval. During the same period, 1,007 Class III products were approved for marketing through the finding that they were substantially equivalent to preamendments Class 111 device types (compare tables 35 and 36). As previously noted, evidence of safety and effectiveness has not yet been required for these postamendments Class III products found substantially equivalent to preamendments devices. Many of these applications for postamendments Class 111 devices are for modifications of devices which were already commercially available.

Postmarketing Surveillance

There are a number of existing and potential methods to monitor hazards associated with the use of devices that have been marketed. FDA maintains a Device Experience Network (DEN) that receives voluntary reports on device hazards; can require repair, refund, or replacement of devices for hazards or defects; and requires that manufacturers keep records of complaints as part of the good manufacturing practices regulations. Two other methods have been mentioned earlier. A condition of approval for new Class III devices approved through the full premarket approval process is that information that manufacturers receive on device defects and adverse reactions has to be reported to FDA within 10 days. And manufacturers, importers, and distributors of devices may be required to provide FDA with information to ensure that their devices are safe and effective.

The major issue in postmarketing surveillance activities has involved the authority that the 1976 amendments gave to FDA to require that information be provided to FDA to ensure that devices already on the market are safe and effective. In late 1980, FDA proposed rules for mandatory device experience reporting, under which manufacturers and distributors of medical devices would be required to submit reports on devices that: 1) may have caused a death or injury, 2) may have a deficiency that could cause a death or injury or that could give inaccurate diagnostic information that could result in improper treatment, or 3) are the subject of a remedial action by the manufacturer (307). Any death that might have been caused by a device would have had to be reported within 72 hours of the manufacturer's or distributor's receipt of that information, with a followup report submitted within 7 working days. Reports also would have had to be submitted within 7 working days after receiving information of any actual or possible device deficiency that could result in a death or injury.

FDA's rationale for a mandatory device reporting regulation was twofold. Practitioners and users of medical devices usually do not report device experiences to FDA but instead contact the manufacturer for information and advice. Reports would be required even if the manufacturer determined that the death or injury was not due to the device or that there was no deficiency, because FDA expected that few devices would be characterized by their manufacturers as having deficiencies, few reports would be submitted, and reporting of confirmed deficiencies would be delayed if manufacturers first investigated before reporting (307).

A year later, in late 1981, the proposed rule was held in abeyance because of comments that the requirements were overly broad and because of issuance in early 1981 of Executive Order 12291 on "Federal Regulation, " under which regulatory actions are to be taken only when the potential benefits of the action outweigh the potential costs. FDA also announced that it would inspect complaint files maintained under the good manufacturing practices regulations to determine if they could be used as an adequate or partial substitute for the proposed rule (309). A pretest, phase I of the review of good manufacturing practices complaint files was completed on December 31, 1981, and phase II started on July 14, 1982, involving a review of the complaint files of 418 firms.

In May 1983, FDA issued a reproposal on medical device reporting, under which reports would be required within 15 days of receiving information that "reasonably suggests, or a person alleges and the manufacturer or importer is aware of the allegation" that one of its marketed devices "has caused or contributed to" a death or serious injury or "has malfunctioned" and, if the malfunction occurs, "is likely to" cause or contribute to a death *or* serious injury (318).

Data analysis of the phase 11 review of good manufacturing practices complaint files had been completed by early 1984, and the report was expected to be available sometime in 1984. FDA has concluded that the good manufacturing practices complaint files would not be an adequate substitute for a mandatory device reporting regulation for several reasons.

First, inspection of complaint files would not lead to timely reporting. Good manufacturing practices inspections are conducted every 2 years, and FDA did not expect more frequent inspections in the future. Second, with over 6,000 establishments to inspect, there would be a problem with deciding which and how many establishments to inspect. Third, the way in which good manufacturing practices records are kept would lead to practical difficulties in collecting the information for adverse experience information. As a consequence, FDA expects to reissue a revised mandatory device reporting proposal in 1984, subject to clearance by the Office of Management and Budget and other Federal agencies (257).

FDA, in its proposals for a mandatory device reporting regulation, has stated that its voluntary reporting system—the Device Experience Network, or DEN—is not an adequate substitute. DEN is not a comprehensive reporting program, and FDA does not have the resources to maintain constant contact with all device users to encourage reporting. Furthermore, device manufacturers are the most knowledgeable about their products and their associated risks and are in the best position to report to FDA. But few manufacturers report under the DEN system, and many of the reports that they make are trade complaints about a competitor's product, not reports from the manufacturers of the devices in question. And in some cases, device manufacturers report device problems to FDA only after a product recall or other remedial action is completed (318).

Reviews of DEN data on Class III devices and of recalls prompted by a hazard with a high likelihood of serious injury or death resulted in the following observations (based on information provided OTA by FDA for the period from 1976 to mid-1983). From the DEN system: deaths allegedly associated with devices were reported most frequently for pacemakers and heart valves; actual injury, reported most frequently with pacemakers, heart valves, IUDs, and to a lesser degree but still relatively frequently, with intraocular lenses; and potential injury, reported most frequently with resuscitation equipment (usually associated with power failure or other electrical malfunction), intra-aortic balloon pumps or catheters, pacemakers, heart valves, and intraocular lenses.

Recalls prompted by risks of serious injury or death were most frequent for cardiovascular devices, with pacemakers again comprising the largest subgroup. Thus, the DEN system and recalls for high risks mostly involve implantable devices, often involve electrical problems, and often involve cardiovascular devices.

The DEN system of voluntary reporting and product recall information do not provide adequate information on the magnitude and frequency of device-related problems. Voluntary reporting also includes allegations of death or injury that may not be associated with the device in question or may be user-related and not due to device defects. FDA also cautions against using DEN for trend analysis, because reports are voluntary, use of the system has changed over time, and the number of reports therefore may reflect trends in DEN participation and other factors (48). However, voluntary reporting does provide indications of the types of devices that have associated risks, and product recall information identifies devices with significant actual or potential risks.

Other Provisions of the Law

Restricted Devices

Section 520(e) of the Medical Device Amendments added a provision for "restricted devices" authorizing FDA to issue regulations imposing restrictions on the sale, distribution, or use of devices. FDA was also authorized to regulate advertising of restricted devices and to inspect manufacturers' records related to restricted devices. Prior to the amendments, the sale and distribution of some devices were authorized only through "prescriptions" by designated persons (e.g., physicians) (21 CFR pt. 801.109). Immediately following the enactment of the law, FDA published a notice announcing that FDA considered "restricted devices" to include all "prescription devices" (303).

When FDA attempted to inspect the records for some prescription devices, however, some manufacturers refused to comply, claiming that FDA had to first issue regulations designating prescription devices as restricted devices. The U.S. District Courts involved in resolving this issue ruled for the manufacturers, and both the First Circuit and Second Circuit of the U.S. Court of Appeals affirmed the decisions of the lower courts (30,171).

As a consequence, FDA decided to issue a regulation rather than attempt to establish through further litigation its authority to inspect records for restricted devices.

The proposed rule on restricted devices was published in October 1980 (305). However, FDA withdrew the proposed rule in November 1981, stating as its reasons: 1) comments that the current prescription device regulation was sufficient, and 2) the February 17, 1981, Executive Order 12291 on "Federal Regulation" that required Federal agencies to undertake regulatory actions only when the potential benefits of the action to society outweigh the potential costs. FDA also stated that it would use the authority for inspection of records required by the good manufacturing practices regulations, as well as the dispensing and labeling requirements of the prescription device regulations, in lieu of a restricted device regulation (309).

Banned Devices

The banned device provision of the law has been used once. Prosthetic hair fibers intended for implantation into the human scalp were banned in June 1983 (319,324).

Color Additives

FDA has not issued regulations on the color additive provisions of the amendments, but the issue has so far been limited primarily to tinted contact lenses. All contact lenses that are required to have premarket approval are also subject to the color additive provisions of the law. FDA initially approved tinted contact lenses even though the color additives had not been listed for that use before the applications were approved (317). When FDA subsequently concluded that it had to apply the color additive provision to tinted contact lenses, it decided that the least unfair method was to complete action on the pending PMAAs and to enforce the provision with future PMAAs (323). FDA is also developing proposed changes in the procedural regulations for color additives to govern their use in all applicable devices (323).

Export of Devices

FDA regulations have not had a great effect on export of medical devices, because most exported devices are those that are legally marketed in the United States and require no special FDA approval.

Most devices requiring FDA approval for export are devices that require but have not yet received premarket approval. The requirement that the importing country approve imports posed some problems because of the possibility that there might not be an official who could give approval. For that reason, FDA has accepted, in lieu of an express approval, a statement from the foreign government that it has no laws prohibiting importation of the device in question. From October 1, 1981 through March 31, 1983, 376 medical devices were approved for export, 13 devices were disapproved, and 1 previous approval was rescinded (181).

Assistance to Small Manufacturers

Both the prevalence and absolute magnitude of regulatory costs increase with establishment size, but the costs of regulations appear more unfavorable to the small manufacturer when costs are considered in proportion to establishment size (197). For example, in a limited study of 30 companies manufacturing only cardiovascular, anesthesiology, or diagnostic products, both initial and recurring costs *per employee* were higher for small plants (fewer than 100 employees) than for larger plants (100 or more employees) (17).

Small manufacturers also are more likely to need assistance in complying with the regulatory requirements. FDA's Office of Small Manufacturers Assistance has received favorable reviews by manufacturers. In a survey of medical device manufacturers, over three-quarters had heard of the office, about half of those who had heard of it contacted it, and more than three-quarters of those contacting the office had found it helpful (197).

DISCUSSION AND CONCLUSIONS

The principal provisions of the statute and FDA's activities have been cataloged above. The 1976 Medical Device Amendments attempted to regulate medical devices in proportion to a device's degree of risk through a number of pre- and postmarketing controls. The amendments placed immediate regulatory priority on significantly new devices while providing a grace period before substantial evidence of safety and effectiveness had to be provided for preamendments Class III devices and their postamendments equivalents.

Section-by-section descriptions and analyses of the major provisions of the Medical Device Amendments and their implementation by FDA were provided above to yield an understanding of the experience so far with the regulation of medical devices. The analysis also identified specific regulatory actions that have been proposed as alternatives to the current situation. However, identifying specific regulatory areas and analyzing the current approaches (and limitations) and their alternatives are not the same as developing strategies (including maintaining the status quo) for medical device regulation. The relative significance of actions that could be taken in specific areas of medical device regulation is hard to determine and justify without relating these actions to more specific strategies than the general rubric of meeting safety and effectiveness objectives at minimal regulatory costs.

In the following analysis, the principal issues that have arisen in implementing the Medical Device Amendments of 1976 are examined. Areas to be discussed include:

- the scope of medical device regulation,
- regulation of preamendments Class III devices and their postamendments equivalents,

- regulation of intermediate classes of devices,
- postmarketing controls, and
- impact of the amendments on medical device firms.

Scope of Medical Device Regulation

FDA has exempted firms from certain requirements of the 1976 Medical Device Amendments; under FDA's IDE regulations, for example, a distinction is made between "significant" and "nonsignificant" risk devices, and sponsors of investigations of nonsignificant risk devices obtain an IDE from an institutional review board rather than from FDA (see section on "Investigational Device Exemptions," above). The law also expressly permits FDA to exempt firms from notifying FDA about their intent to market selected devices, and FDA has done so for selected types of Class I devices, subject to minimal recordkeeping requirements.

The Scientific Apparatus Makers Association had petitioned FDA to drop notification requirements for Class I devices, claiming that Class I devices would still be subject to the registration requirements and surveillance under the good manufacturing practices regulations. FDA subsequently denied the petition on the grounds that the legislative intent was to make decisions on the basis of generic types of devices, and not whether or not devices were in a specific class (see section on "Premarket Notification," above).

Rather than being considered on the basis of the present statute's legislative intent, the proposal for dropping notification requirements for Class I devices could be reconsidered in a reassessment of the statute. With over 7,000 device establishments registered with FDA, listing approximately 41,500 products representing over 1,700 device types, one important question that arises is whether the scope of present device regulation is too broad. Not only could regulatory costs be excessive when information is gathered that is not going to be used, but other activities undertaken to help assure safety and effectiveness could be curtailed because of competition for funds within a limited FDA budget.

Regulation of Preamendments Class III Devices and Their Postamendments Equivalents

As of early 1984, classifications had been completed for device types in 11 of the 19 medical specialty categories, and proposed regulations, most initially issued in 1982, had been issued for those in the remaining 8 (see table 34). As preamendments Class III devices and their postamendments equivalents cannot be required to show substantial evidence of their safety and effectiveness until at least 30 months after final classification, it will be 1986 at the earliest before manufacturers of devices in the eight medical specialty categories without final classifications can be required to show that their products are safe and effective.

FDA could have expedited classification of high-priority device types within each medical specialty category instead of waiting to classify all devices within each category. For example, the classification process for device types that had been provisionally designated Class 111 could have been completed first, thereby starting the clock on the 30-month grace period.

On the other hand, the medical specialty categories for which FDA first issued final classifications (see table 34) include the categories in which most of the deaths and injuries were found in a review of the literature by the Cooper Committee before the amendments were enacted—i.e., cardiovascular (heart valves, pacemakers) and obstetrics-gynecology (IUDs). Devices in these categories continue to be the major causes of death or serious injury as reported in FDA's voluntary DEN reporting system (see section on "Postmarketing Surveillance," above). Thus, the medical specialty categories for which FDA has completed classification include those categories containing devices with the highest known risks.

Related to classification of preamendments devices is the regulation of similar postamendments devices through application of the "substantial equivalence" clause and the practice of "equivalence creep" or "piggybacking" whereby a postamendments device can be found "substantially equivalent" to another postamendments device that had been previously found to be substantially

equivalent to an actual preamendments device. One issue is the safety and effectiveness of postamendments Class III devices that have been permitted to be marketed through the "substantial equivalence" route, because the preamendments devices against which they have been compared have yet to be required to show evidence of their safety and effectiveness.

After the 30-month grace period for preamendments devices expires, if FDA requires evidence of safety and effectiveness for their continued marketing, more evidence on safety and effectiveness will be available on the preamendments devices with which postamendments devices are compared. Each manufacturer of a Class III device, whether pre- or postamendments, would have to submit a PMAA if required, because FDA cannot consider the evidence of safety and effectiveness in one application when reviewing another device, even one that was previously found substantially equivalent.

As discussed earlier, FDA has initiated proceedings for some preamendments Class III devices for which the grace period has ended and which FDA has determined have the highest need for evidence of safety and effectiveness (e.g., the implanted cerebella stimulator). Criticisms of the pace at which FDA classified preamendments devices, which determines when evidence of safety and effectiveness of preamendments Class III devices could be required, could have been muted if the classification process had been speeded up for preamendments Class III devices in all categories. Final classification of preamendments devices is no longer a major issue, however, because classifications have already been proposed for those medical specialties without final classification (see table 34), and final classification should occur soon.

The remaining issues are: 1) what type of safety and effectiveness evidence should be required for preamendments Class 111 devices; and 2) how the "substantial equivalence" clause should be applied by FDA. FDA, in announcing its intent to require safety and effectiveness evidence for those preamendments Class III devices it has identified as having high priority, indicated that it intended to ask for data of the type needed for premarket approval of new postamendments Class 111 devices (321). However, for less controversial preamendments devices, more flexibility in the types of evidence that have to be provided maybe appropriate. As for the application of the "substantial equivalence" clause, other interpretations or other methods of approving postamendments Class III devices are possible (see "Policy Options" section below).

As noted above, the regulations that FDA has issued on IDEs distinguish between "significant risk" devices, for which sponsors have to receive express approval from FDA to conduct studies under an IDE, and all other Class III devices, of whose testing FDA need not be actually informed and which are considered to have approved IDEs subject to certain conditions (see section on "Investigational Device Exemptions, " above). This distinction reflected express statutory authority and a decision by FDA that risks from Class III devices varied and monitoring of testing should reflect the degree of risk.

FDA has also indicated that IDEs will be made available to manufacturers of preamendments Class III devices so that they can continue to market their devices if they cannot provide reasonable assurance of safety and effectiveness when FDA requests such information. In its "Notice of Intent to Initiate Proceedings to Require Premarket Approval of Preamendments Devices," FDA has stated that within 90 days of the issuance of a final regulation, a PMAA must be filed or commercial distribution has to cease.

But an alternative for the manufacturer is to obtain an IDE and continue distribution for the limited purpose of obtaining safety and effectiveness data from clinical trials. In addition, under section 515(6) of the amendments, FDA can extend the grace period if it finds that "the continued availability of the device is necessary for the public health" (321).

The rationale for this use of the IDE is weak. Manufacturers of preamendments devices have had years to prepare to substantiate the safety and effectiveness of their devices, because the law was passed in 1976, the classification process is still not over, and there is a 30-month minimum grace period from the date of final classification.

Regulation of Intermediate Classes of Devices

For several reasons, Class II designation has probably received the most attention. First, Class II represents the important middle ground of the whole regulatory approach. Second, the majority of device types have been placed in Class II (more than 1,000 out of over 1,700; see table 34). And third, no performance standards have yet been issued.

Regardless of whether or not the 1976 statute requires, rather than permits, the use of performance standards, the fact remains that, as a practical matter, there is little possibility that standards can be formulated for the large number of device types that have been placed in Class II. If performance standards were meant to be selectively used, the designation of so many device types as Class 11 and the resulting perception of the futility of such an exercise have been damaging to FDA's efforts, no matter what the rationale.

At the least, the present situation points out the need for an intermediate regulatory class, the inappropriateness of mandatory performance standards as the sole or even principal method of regulation, and the need for other methods of regulating intermediate devices.

There are, of course, many ways of regulating an intermediate class of devices. The principal issues here are: 1) whether a change in the statute is needed before FDA can use other than performance standards, and 2) what types of regulatory controls could be used.

Postmarketing Controls

Postmarketing controls on medical devices are of two types: 1) removal from the market or restrictions on the sale, distribution, or use of designated devices; and 2) postmarketing surveillance of the clinical experiences with medical devices.

FDA can remove a device from the market by requiring repair, refund, or replacement; by banning it; or by revoking any approval to market the device. There are two types of restrictions on the sale, distribution, or use of a device. The first is a restriction to prescription sale or use, applied when adequate labeling for lay use cannot be written or when special skills or training are required, such as diagnosing a disease or condition or prescribing for treatment. The second is a restriction based on other conditions FDA may prescribe in regulations in order to provide reasonable assurance of the safety and effectiveness of the device.

The restricted device regulations were withdrawn by FDA with the explanation that the prescription device regulations were adequate. In addition, Executive Order 12291 requires that Federal agencies undertake regulatory actions only when the potential benefits outweigh potential costs. However, in the original proposed regulation, FDA had stated that (305):

> . . . the current determination that a device is a "prescription" device is quite subjective. Often, the determination is made by the manufacturer.

FDA therefore proposed the restricted device rule to make these criteria more objective.

FDA also stated in its withdrawal of the proposed restricted device rule that it would use its inspection authority under the good manufacturing practices regulations to inspect manufacturers' records on these types of devices for information on such matters as deaths and injuries (309). But the Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee observed that (338):

> . . . most of the general controls . . . are geared toward ensuring that finished devices, when ready for use, will be free from defects, safe and effective. Restriction, on the other hand, can address problems with a device once it is in use. It deals with the risks that practitioners, technicians, or others who employ the device are doing so improperly due to inadequate training, experience, facilities, or instructions.

These issues—use of existing sources of information on deaths and injuries, and problems arising from improper use of medical devices rather than from improper manufacture—have also been involved in the debates on the types of postmarketing monitoring activities that should be conducted.

One of the expressed reasons why mandatory device reporting regulations have been held in abeyance was to examine whether the complaint

files which are required under the good manufacturing practices regulations could partially or completely substitute for the mandatory device reporting regulations. As described earlier, the examination had been completed by early 1984, with the conclusion that the good manufacturing practices complaint files are not adequate substitutes for mandatory reporting (257).

On the question of improper use, the General Accounting Office has recommended that FDA's voluntary DEN reporting system be revised so that information is included on the scope and nature of device problems caused by user error and inadequate maintenance; that the data be analyzed to identify special problems, areas where problems might be concentrated, and trends; and that the results be used to aid in developing solutions. FDA responded that these recommendations would be taken into consideration and that possible actions would include implementing educational programs or restricted use criteria (331).

Thus, FDA may eventually issue restricted device regulations, subject to the current administration's position on deemphasizing regulatory approaches and its preference for voluntary initiatives. Furthermore, efforts may be made to upgrade the voluntary DEN system and disseminate that information to educate users about potential hazards.

Impact of the Amendments on Medical Devices Firms

The preceding analyses examined individual provisions of the 1976 Medical Device Amendments and their implementation by FDA. A broader issue is the impact of the amendments on the medical devices industry. Information available on the impact of the law reflects regulatory implementation by FDA and understanding of the law by device firms in the first few years following passage of the statute. In evaluating this impact, it is important to keep in mind that some sections of the amendments have been implemented fully, some partially, and some have yet to be addressed.

Two studies that FDA conducted to establish "baseline conditions" in order to track changes that occur in the future were summarized earlier, based primarily on 1977 data (391,392). These studies showed that the "medical devices industry" is quite heterogeneous. There is a clear separation of the industry into medical device versus diagnostic testing firms, with little overlap between manufacturers of either type of product.

The medical device portion of the industry is further separable into establishments that are highly specialized and those that manufacture devices in several areas. Sixty-four percent of manufacturers made devices in only one device area. Highly specialized areas include dental, ophthalmic, and radiological devices.

Each device type is made by an average of nine different manufacturers, but this measure of "product availability" or "concentration" in the industry is related to the class of the device. Class I device types averaged 13.1 manufacturers per type; Class II,. 7.9 manufacturers; and Class III, 4.5 manufacturers. Devices made by only one or two manufacturers ("exclusive" devices) comprised 28 percent of all device types and followed a similar pattern. Only one or two establishments were manufacturing 41 percent of the Class III device types, compared to 28 percent of Class II device types and 24 percent of Class I device types.

Large establishments were more likely to make: 1) more device types, 2) an "exclusive" device, 3) a Class III device, or 4) a "critical" device (defined by FDA as requiring more rigorous controls in the manufacturing process).

These findings lead to the following observations. First, the distinction between firms that manufacture diagnostic tests and firms that manufacture other medical devices probably reflects the "catchall" nature of the 1976 Medical Device Amendments, which essentially authorized Federal regulation over all medical products that are not drugs or biologics. One question is the appropriateness of regulating such distinctly different products in a similar manner. For example, Class III medical devices are generally those that are implanted or have life-support or life-sustaining functions, and criticisms of FDA's application of the law to devices of this nature have been raised when FDA has chosen not to place some of these types of devices in Class 111 (253).

On the other hand, diagnostic tests pose few direct risks, but some have been placed in Class III because defective tests could lead to erroneous treatment (or no treatment), which in turn could result in harm to patients. The underlying questions are whether the law's scope and application are appropriate, and if not, whether regulation of diagnostic tests and other medical devices can be addressed differentially under the present law or whether new legislative remedies should be explored.

Second, it should be remembered that the findings that devices in higher regulatory classes have fewer manufacturers per device type and that larger manufacturers are more likely to manufacture devices in a higher regulatory class represent the situation that was already present before the amendments were implemented. Classification under the 1976 amendments did not *cause* but might be expected to *reinforce* this situation, especially for Class III devices, because of the higher costs associated with approval.

FDA also commissioned a survey conducted in the fall of 1981 of medical device manufacturing establishments that had been registered with FDA in September 1980 (197). The surveyors concluded that there was no evidence that the amendments raised barriers to market entry, reduced innovation, or adversely affected investment, sales, or employment. For example, one of the survey's conclusions, based on information provided by the surveyed manufacturers, was that there was no evidence that patent activity had measurably declined since the Medical Device Amendments were enacted in 1976.

Figures 2 and 3 provide a more comprehensive picture of medical device patent activities, summarizing patent applications with the U.S. Patent Office between 1968 and 1979. Patent applications on "low-technology" devices such as bandages, receptacles, eyeglass frames and lenses began leveling off just prior to the 1976 amendments. But applications for "high-technology" devices such as implants, dialysis machines, respiratory devices, and cardiovascular devices continued to increase throughout the decade (see app. D)

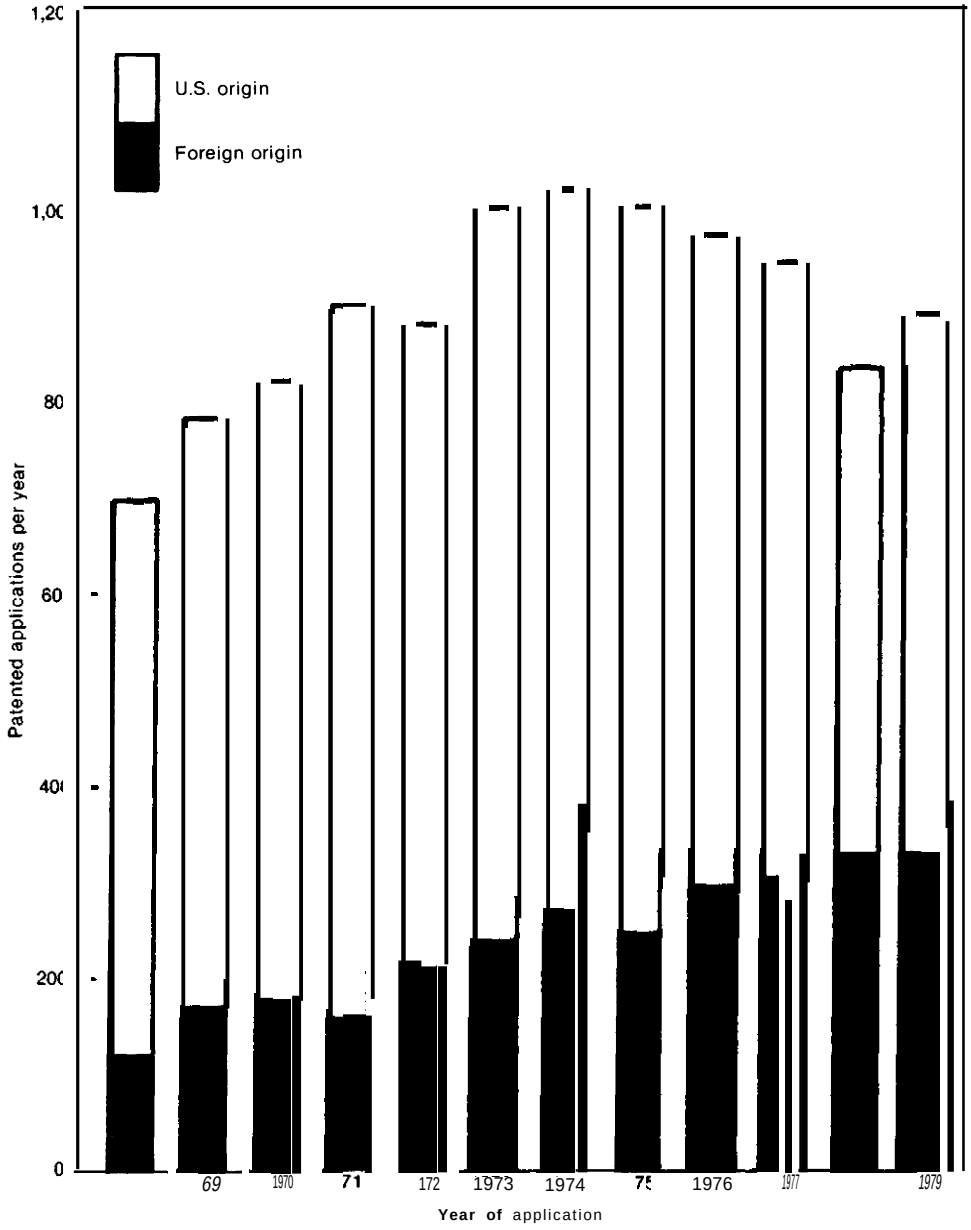
The 1981 survey commissioned by FDA found that a third of all manufacturers had entered the medical device field ***after*** the 1976 statute (197). Most manufacturers reported increases in domestic and foreign sales, research and development (R&D) activities, and the number of new devices introduced since the amendments. Fifty-one percent were more profitable and only 27 percent less profitable than they had been prior to passage of the amendments, and 80 percent were optimistic about doing business in medical devices during the next decade.

The survey also found that significant R&D activities were common traits in medical device firms—whether they were large, medium, or small—and that the introduction of significantly new medical devices had been just as common for small firms as for large firms (197). But when the survey was conducted in the fall of 1981, only a quarter of small establishments (1 to 9 employees)—as compared to 63 percent of establishments with over 500 employees—reported that they would consider developing and marketing a Class III device. The surveyors concluded that Class III designation appears to be more likely to discourage small establishments than large establishments from developing new devices, but observed that opinions do not necessarily translate into behavioral differences. They pointed out that 8.4 percent of establishments were manufacturing Class III devices and that a higher percentage of manufacturers would continue developing Class III devices.

Somewhat in contrast with the overall optimistic picture of the industry just presented were manufacturers' answers to the survey question of the impact of the Medical Device Amendments (197). Nearly half (46 percent) stated that Federal regulation had been a major problem for them, and 21 percent stated that regulation was the single most serious problem. However, although most manufacturers wanted changes in the regulations, they did not believe (53 percent) that device regulation should be abolished, and the vast majority (80 percent) believed that at least implants and life-support or life-sustaining devices should be strictly regulated.

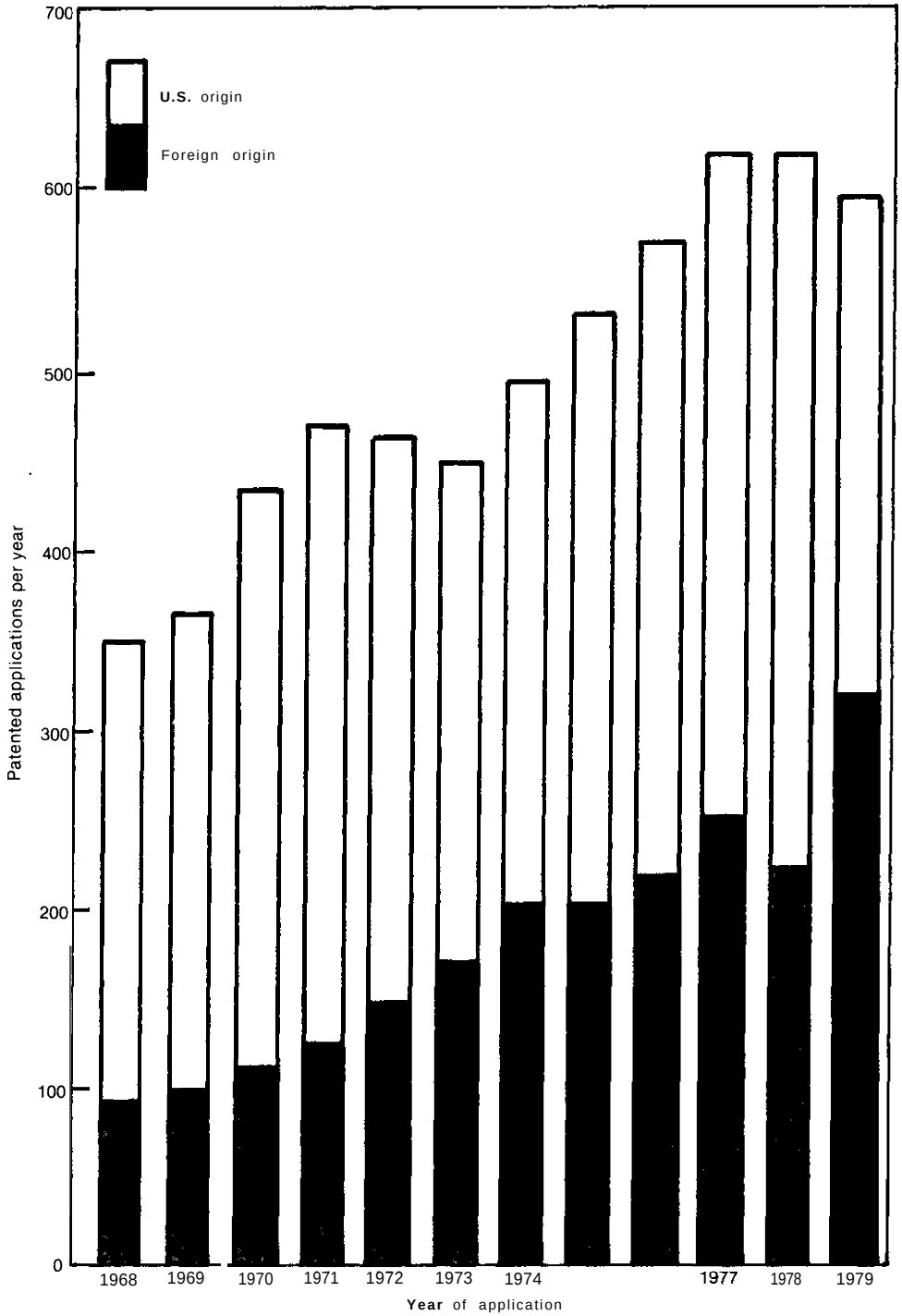
The specific problems associated with regulation under the 1976 amendments were varied (197). One problem reported by a substantial

Figure 2.–U.S. Patent Applications for Low-Technology Medical Devices, 1968-79



SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration, Office of Economic Analysis, Rockville, MD, compilation of unpublished data from the U.S. Patent and Trademark Office, December 1983.

Figure 3.–U.S. Patent Applications for High-Technology Medical Devices, 1968-79



SOURCE: U.S. Department of Health and Human Services, Food and Drug Administration, Office of Economic Analysis, Rockville, MD, compilation of data from the U.S. Patent and Trademark Office, December 1983.

number of manufacturers in the 1981 survey was the cost of compliance. In order to meet the regulatory requirements, 64 percent either added new employees, purchased new equipment, or increased outside purchases. Absolute costs increased with establishment size, but when adjusted for establishment size, smaller manufacturers had relatively higher costs per employee in meeting the regulatory requirements.

Another problem reported by a significant number of manufacturers was in understanding what to expect from FDA in meeting the regulatory requirements. Of particular interest is the correlation between manufacturers' attitudes toward FDA and their understanding of the regulations. Of those manufacturers who said they fully understood the regulations, about half (51 percent) gave FDA a positive rating, and 71 percent stated that the regulations were effectively protecting the public. The Office of Small Manufacturers Assistance was one FDA information source that was positively received by the industry, but difficulty in understanding the regulatory requirements was still a major problem and fell disproportionately on small manufacturers. Thus, a particular priority for regulatory reform was in special efforts to improve manufacturers' understanding of the device regulations.

Despite the negative opinions by manufacturers regarding regulation, majorities still reported that registration, product listing, product classification, labeling requirements, premarket approval, and IDEs had no effects on their establishments (197). Seventeen percent of manufacturers even reported that good manufacturing practices have been of help to them.

Under the 1976 amendments, difficult and complex precedent-setting decisions have been made on a diversified industry that was not previously subject to a great deal of FDA regulation. In general, the 1976 Medical Device Amendments have not had a significant negative impact on the manufacturers of medical devices. Particular segments of the industry may be more affected than others, however, and compliance costs affect small manufacturers relatively more than they do large manufacturers.

In the contact lens industry, the issues of the costs of complying with regulations and small manufacturers' entry into the market have converged (see discussion under "Reclassification of Devices" section, above). Class III designation of new types of contact lenses (soft lenses, gas-permeable lenses) has made it difficult for many small companies to gain early entry because of the costs of gathering clinical evidence on safety and effectiveness. But there has not been a unified front by the contact lens industry against Class 111 designation. Rather, large firms that already have market approval have tended to resist reclassification from Class III to Class I or II. At issue in this instance is competition between first entrants into the market and subsequent manufacturers. The public policy goals that are at odds are rewarding companies that first succeed in getting innovations on the market versus achieving greater availability of products of a particular type, with price competition as one result.

Throughout the medical devices industry, one of the impacts of medical device regulation has been uncertainty over the regulatory requirements. This situation, in retrospect, is understandable, given the fact that the implementation

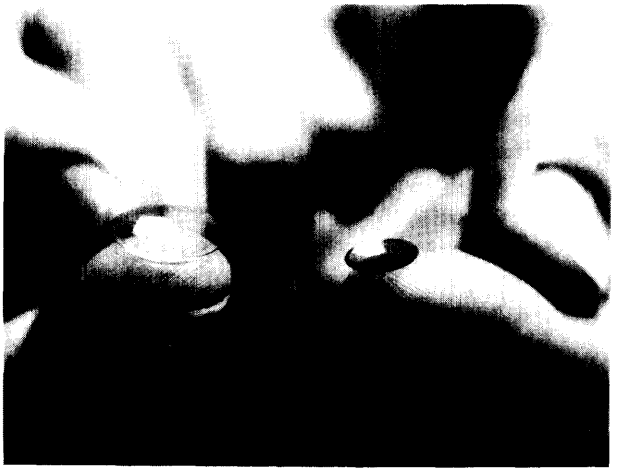


Photo credit: Bausch & Lomb SOFLENS, Professional Products Division

The new generation of contact lenses, such as the soft contact lens show on the left, are subject to the full premarket approval process of the Food and Drug Administration. The older types of hard contact lenses, such as that shown on the right, no longer have to go through the full premarket approval process.

of some provisions of the law has not been initiated or completed and the fact that the majority of devices have been placed in Class II, despite inability to proceed with the statutory intent of regulating this class of devices through performance standards.

Conclusions

During the 8 years since the Medical Device Amendments of 1976 were enacted, the medical devices industry has continued to grow, and while regulatory costs have been incurred, regulation has generally not had a significant negative impact on the industry. A large part of the industry's development may be due in part to FDA's implementing the 1976 law in ways that would make market entry easier—as in use of the 510k premarket notification and a finding of "substantial equivalence" as the predominant route for devices to be released for marketing—and in part to FDA's not implementing or implementing slowly some of the law's provisions. The situation for industry may change if FDA implements all of the provisions of the amendments, or as new medical devices are developed that make it harder over time to use the "substantial equivalence" route to market devices.

Several provisions of the amendments that are targeted at specific risk categories—such as those pertaining to the safety and effectiveness of preamendments devices, regulation of Class II devices, and monitoring of devices once they are on the market—have yet to be fully implemented or addressed. Yet there is little information that *actual* risks are systematically occurring or not being addressed by FDA's choice of priorities in implementing the amendments.

This paucity of information on actual risks can be interpreted in two ways, based on opposing assumptions. First, it might be taken as an indication that hazards are in fact low, that the current application of the amendments is satisfactory, and that it is not necessary to implement all of the law's provisions. An alternative interpretation is that the paucity of information on risks is a deficiency in itself—one that the amendments attempted to address—and that a lack of information on risks is a problem that needs to be addressed.

The Medical Device Amendments provided more effective methods for dealing with fraudulent devices, and the increasingly complex nature of "high-technology" medical devices was one of the imperatives for developing premarket screening and testing requirements. Public policy in these two instances was not primarily dependent on quantifying the number of injuries currently caused by medical devices. In the case of fraudulent devices, the amendments provided more effective tools for removing these devices from the market. For "high-technology" devices, the amendments attempted to anticipate and minimize potential risks associated with their use through pre- and postmarketing controls. Realistically, however, it might be expected that debates over how and to what extent medical devices should continue to be regulated will focus on the costs to industry versus (lack of knowledge of) the extent of risks associated with medical devices.

In sum, 8 years after the Medical Device Amendments of 1976 were enacted, the medical device industry has incurred regulatory costs but continues to prosper in general; major sections of the law remain partially or not implemented, and there do not seem to be any obvious, major risks that are not being addressed, a situation that may reflect either a lack of significant risks or lack of knowledge of significant risks that do exist.

POLICY OPTIONS

Most of the attention that has been focused on medical device regulation since the enactment of the 1976 Medical-Device Amendments has been oriented toward questions such as whether a particular provision of the 1976 law has been implemented, whether its implementation has been compatible with congressional intent, and whether the provision worked in practice as it did in con-

cept (331,338). A range of options proposed for specific issues that the current law was designed to address is provided below. Areas of the law to be specifically addressed include:

- evaluating the safety and effectiveness of preamendments devices and their postamendments equivalents,
- developing performance standards for Class II devices,
- reviewing postmarketing activities and controls, and
- assisting small manufacturers of devices.

Beyond developing options on specific provisions of the law, however, there is the question of how specific actions fit within an overall regulatory framework. Various overall regulatory approaches are presented in the first three options below.

Scope of Medical Device Regulation

Option 1: Continue the basic framework and intent of the 1976 *Medical Device Amendments and make adjustments in implementation or wording of the specific provisions of the law.*

A judgment could be made that the basic framework and intent of the 1976 amendments remains appropriate and that the law's implementation by FDA should proceed, subject to modifications in the wording or implementation of specific provisions of the law that reflect judgments on the appropriate balance between methods of ensuring safety and effectiveness and the costs associated with these methods.

FDA, in implementing the 1976 law, has had to develop a set of priorities so that its limited resources could be efficiently applied. Congress could provide more direction to FDA on what it considers priority issues and what orientation it considers appropriate within a particular regulatory area. Setting such priorities would entail weighing benefits to consumers from reducing risks and ensuring efficacy versus costs to the industry from regulatory requirements. Examples of priority areas might include approval of new devices, particularly Class III; safety and effectiveness of preamendments Class III devices; selective monitoring and controls over marketed devices; and development of better information on device-associated risks.

Congress could also provide direction within each priority area on the extent of its concern about ensuring safety and effectiveness versus minimizing barriers to market entry. Approaches to balancing safety and effectiveness versus ease of marketing are reflected by the variation in the types of safety and effectiveness evidence that could be required for preamendments Class III devices and in whether FDA or device manufacturers should bear the burden of proof (see Options 4, 5, and 6).

A different strategy from focusing on which provisions of the law should be emphasized would be for Congress to determine which aspects of the current law do *not* have high priority. The exemption of devices from some of the law's requirements through the use of FDA's discretionary authority has been previously discussed. FDA has exempted manufacturers of some Class I device types (e. g., specimen containers) from having to notify FDA when they intend to market their devices and from most of the recordkeeping requirements of the good manufacturing practices regulations. In the regulations on IDEs, FDA makes a distinction between "significant risk" and "nonsignificant risk" Class 111 devices and requires different procedures for the two. Also mentioned earlier was a petition to FDA from the Scientific Apparatus Makers Association, subsequently denied by FDA as being against legislative intent, to drop 510k notification requirements for *all* Class I devices.

Option **2:** *Revise the* 1976 *Medical Device Amendments to reflect the status quo with regard to FDA's implementation of the law.*

Although the issuance of mandatory performance standards for Class II devices has proved not to be feasible and FDA has yet to complete the implementation of several other provisions of the 1976 law, obvious, systematic deficiencies in the safety and effectiveness of medical devices have not been apparent. One approach, therefore, might be to recognize the two-tiered regulatory approach that has been applied to medical devices rather than the three-tiered approach originally built into the law.

More flexibility could be obtained through the kinds of controls identified previously to augment or replace Class II performance standards (see Option 13), but the bedrock of the law could be limited to: 1) general controls for all devices, and 2) premarket approval requirements for a limited number of devices, such as implantable or life-supporting devices. Other current provisions could also be modified or deleted. For example, review of preamendments devices could be limited to high-priority device types, the approach that FDA is currently taking.

Option 3: Revise the 1976 Medical Device Amendments to exclude certain device types from regulation.

In the previous option, revisions in the law would be guided by FDA's implementation of the law to date. In addition to or in place of that option, Congress might choose to consider statutory exclusions of some device types.

Statutory modifications could be guided by focusing on risks, such as the proposal to exempt Class I devices from notification and recordkeeping requirements, or by focusing on the variety of medical products currently under the jurisdiction of the amendments, such as the question of whether it is appropriate to regulate diagnostic tests in the same manner as other types of medical devices.

Regulation of Preamendments Devices and Their Postamendments Equivalents

The 1976 amendments provided a 30-month grace period after final classification before evidence of the safety and effectiveness of preamendments Class III devices would be required by FDA. For these devices, two issues that remain are what type of evidence has to be presented and when that evidence has to be provided to FDA. In part, these issues are important because of the widespread use of the "substantial equivalence" method of gaining market entry for postamendments devices. As previously discussed, a finding of substantial equivalence will be made if a new device does not differ markedly as to materials, design, or energy source, and if there is no significant difference with regard to safety and effectiveness. As yet, however, there is no requirement to provide safety and effectiveness evidence on the preamendments devices with which new devices claimed to be their substantial equivalents are compared.

In addition, FDA's Office of General Counsel does not consider a finding of "substantial equivalence" an approval. A device is considered approved once a determination is made that it is safe and effective. The 510k method of obtaining FDA's permission to market a device is basically a determination that the device is substantially equivalent to a preamendments device, and FDA has no choice but to allow it to be marketed; it IS not a determination that the device is safe and effective **(464).**

ISSUE:

What evidence of safety and effectiveness should be required of preamendments Class III devices?

Option 4: Continue FDA's current approach of emphasizing safety and effectiveness evidence for high-priority preamendments Class III devices.

Under FDA's current policy as represented by this option, preamendments Class III device types with questionable safety and effectiveness or with relatively high risks will be addressed by FDA first, using expert opinion and publicly available literature. This approach can be viewed as a reasonable allocation of FDA's limited resources, although FDA has to gather and review information to set areas of priority, and developing the information can be very resource-intensive for FDA

Option 5: Limit through legislation requirements for evidence of safety and effectiveness of preamendments Class III devices to device types that have specific problems associated with them.

This option would codify FDA's current approach so that FDA would *have* to identify preamendments Class III device types with problems before it could require evidence of safety and effectiveness. Other preamendments device types

would be presumed to be safe and effective, subject to development of new information. As in the previous option, this approach could be resource-intensive for FDA because the agency would have to gather evidence to identify problem devices. Legislating this approach instead of relying on FDA's discretion would reduce uncertainty and make it explicit that all preamendments Class III devices will not eventually have to show evidence of safety and effectiveness.

Option 6: Encourage FDA to accept evidence of safety and effectiveness such as reviews of the literature and expert opinion, in lieu of clinical evidence, for preamendments Class III devices.

In the two previous options, the safety and effectiveness of preamendments Class III devices would in effect be presumed, and FDA would develop information to counter that presumption before initiating actions. In this option, the burden of providing FDA with evidence of safety and effectiveness would continue as now to rest with the manufacturers, but the range of acceptable types of evidence would be greater. This approach would enable FDA to screen all device types or a greater number than would the two previous options, and the screening process might then be used by FDA to target problem devices.

A variation of this option would be for FDA to start with the presumption that clinical data on devices are required but allow manufacturers to overcome that presumption with evidence gained from general use of these types of devices.

ISSUE:

When should safety and effectiveness evidence be required of preamendments Class 111 devices?

Option 7: Continue FDA's interpretation that the end of the 30-month grace period after final classification establishes the earliest date that FDA can require safety and effectiveness evidence on preamendments Class III devices.

Because the 30-month grace period establishes the earliest date on which the agency can act, FDA has begun the process of requiring safety and effectiveness evidence for only a few "high-priority" preamendments Class 111 devices. FDA's priority-based review is dictated by the limited resources available to FDA and the resulting difficulty in calling for evidence of safety and effectiveness for all preamendments Class 111 devices as their grace periods expire. Thus, the issue of *when* such evidence will be required is related to the question of what *kinds* of evidence will be acceptable (see Options **4, 5,** and 6).

Option 8: Establish the end of the 3&month grace period after final classification as the time when FDA has *to call for safety and effectiveness evidence on preamendments Class III devices.*

This option could be legislated, but its desirability depends on whether FDA takes other approaches to ensuring safety and effectiveness as discussed above and on the resources FDA could devote to preamendments devices relative to other provisions of the law. For example, if FDA takes the approach in Option 6 of accepting a greater range of evidence to screen for problem devices, this option would be much more reasonable to implement than under current conditions, in which FDA has assumed responsibility for identifying problem areas.

Option 9: Prohibit use of the IDE to extend the grace period for preamendments Class III devices that have been required to show evidence of safety and effectiveness, except when no acceptable alternatives are available.

The grace period for many preamendments devices had not ended or had not even begun as of early 1984, 8 years after the amendments were passed. Given this extended period of "notification," there seems little justification for making IDE routinely available to preamendments device manufacturers. Possibly, however, IDEs could be made available on a case-by-case basis. Routine use of the IDE to continue limited distribution of preamendments devices would be less of an issue if other types of evidence of safety and effectiveness, such as literature reviews and expert opinions, were accepted.

Except for those options specifically calling for legislation, all of the options pertaining to preamendments Class 111 devices could be implemented under the existing statute. However, Congress could mandate a particular approach through legislative changes.

ISSUE:

Does the "substantial equivalence" method of entering the market for postamendments medical devices need to be revised?

The 1976 Medical Device Amendments require that any postamendments device not found "substantially equivalent" to a preamendments device be automatically classified in Class III, with subsequent opportunity to petition for reclassification of the device in Class I or II. The "substantial equivalence" clause of the 1976 law was meant to make a regulatory distinction between those postamendments devices that are modifications of commercially available devices from those that are truly new devices.

Because of the costs and delays in approval associated with the reclassification process, however, manufacturers of postamendments devices have had incentives to seek a finding of "substantial equivalence" rather than reclassification so that they can market their devices much sooner. Much less information is needed to successfully claim that a postamendments device is substantially equivalent to a preamendments device than to gain approval through the premarket approval process. In fact, the lack of information on the safety and effectiveness of preamendments devices raises questions about how determinations of substantial equivalence can be made.

Option 10: Retain existing procedures for determining 'substantial equivalence. "

As previously explained, FDA has begun to call for safety and effectiveness evidence on high-priority preamendments Class III devices, and once that evidence is presented and evaluated, there should be a substantive basis for comparing these devices with postamendments devices determined to be substantially equivalent. But the process will take years and may be selective rather than including all preamendments Class III devices.

On the other hand, the "substantial equivalence" clause has been a convenient method for device manufacturers to get their products onto the market quickly But as new generations of postamendments devices diverge more and more from their preamendments antecedents, it will be harder for manufacturers to use the substantial equivalence method of market entry. It will also be harder to practice "piggybacking," in which a postamendments device is compared to another postamendments device and, through a chain of other postamendments devices, eventually compared to a preamendments device.

More immediately, FDA's Office of General Counsel has stated that such "piggybacking" is not authorized by the amendments (464), and if the practice of piggybacking ceases, more postamendments devices will eventually be placed in Class III, and their manufacturers will have to go through the full premarket approval process or petition FDA for reclassification.

Option 11: Eliminate automatic classification into Class III of postamendments devices that are not found substantially equivalent to preamendments devices, and allow FDA to place a device in the appropriate class at the time of notification.

Automatic classification into Class 111 of postamendments devices that are not found substantially equivalent to preamendments devices serves as a second screen in the regulation of post-1976 devices. The first screen is a determination of whether or not a device is "substantially equivalent" to a preamendments device. The second screen, with automatic classification into Class 111, is a presumption that any device that is not substantially equivalent needs full premarket approval, unless the manufacturer successfully petitions FDA for reclassification in Class I or Class 11 Under this option, the burden of responsibility of coming forth with evidence that rebuts initial Class 111 designation could remain with device manufacturers, but manufacturers could be allowed to present this evidence for classification at the time of notification. This change should reduce current incentives to claim "substantial equivalence. "

Option 12: Develop approaches for reviewing new devices that are different from those for reviewing modifications of commercially available devices.

Eliminating automatic Class 111 designation of postamendments devices that are not found substantially equivalent to preamendments devices might serve to bring out the distinction between modified and new devices that the "substantial equivalence" clause was originally meant to provide. GAO has recommended another approach, eliminating the "substantial equivalence" clause so that all Class 111 (but not Class I or II) postamendments devices have to go through premarket approval. (Automatic Class III designation for non-substantially equivalent postamendments devices could also be eliminated so that new devices that would more appropriately be put into Class I or II would not have to go through the superfluous step of reclassification.) In general, then, the difference in approach could be between pre- and postamendments devices as originally intended, or between Class III pre- and postamendments devices, where the difference in regulatory requirements is most pronounced.

Regulation of Class II, or Intermediate, Devices

More than 1,000 of the 1,700 device types have been placed in Class II. The unanimous opinion, however, is that except for a small number of device types, performance standards cannot be developed in a timely fashion. Thus, if an intermediate class of regulation is still needed, performance standards will have to be replaced by other types of regulation between Class I and its good manufacturing practices requirements and Class 111 and its premarket approval requirements.

Option 13: Give FDA legislative authority to use available methods in addition to performance standards to regulate Class II devices.

An obstacle to the use of methods for regulating Class II devices other than performance standards has been the question of whether or not the law *requires* the use of performance standards. GAO has in fact suggested that the law be revised to give FDA the authority to make a device-by-device determination of when performance standards are needed (331). Although the use of performance standards may not be mandatory, a change in the statute clearing up the ambiguity might be useful in setting into motion substantive efforts to use other approaches, instead of continuing to focus attention on the unrealistic expectation that so many performance standards can be developed.

FDA has suggested using a combination of voluntary standards, user education, and other existing controls to regulate Class II devices (387). Previously identified controls include revoking any approval to market a device, banning the device, or requiring repair, refund, or replacement, and the prescription and restricted device provisions. If the legality of using available approaches in place of performance standards is upheld or the use of these remedies legislated, a three-tiered regulatory system for medical devices can be put in place. Rather than a Class II with mandatory controls, however, there would be specific devices (Class I or Class III) for which additional controls could be stipulated (e.g., prescription or restricted devices), and device-by-device determinations of the applicability of these other controls.

Option 14: Legislate an additional category of Class II devices to be regulated through methods other than performance standards.

The Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce has suggested that performance standards be retained for Class II and that a Class 11A be formed on which greater controls (e.g., restrictions under the restricted device clause, increased mandatory device experience reporting, and adoption of performance specifications against which the device must be tested periodically) are imposed (338).

This option is similar in effect to the previous option, the principal difference being that this option involves legislating an explicit, additional category of Class II devices and retaining mandatory performance standards for some devices. Also, this option would leave less discretion to FDA in determining which devices should be regulated and how they should be regulated.

Option 15: Encourage FDA to reclassify most Class II device types into Class I or III and to continue to develop performance standards for the remaining Class II devices.

Rather than being regulated through performance standards, medical devices receiving Class

II designation are currently being regulated by FDA as though they were Class I devices. A partial approach to the problem might be to screen current Class II devices to see whether some of them could be placed in Class III. This issue was raised by the Health Research Group in the case of General and Plastic Surgery devices, when FDA proposed placing seven implantable device types (including artificial ears, noses, and chins) in Class II rather than Class III (253).

The burden of regulation under Class III for reclassified Class II devices might not be onerous. FDA already differentiates between "significant risk" and "nonsignificant risk" Class III devices in its IDE regulations; and FDA could develop different levels of evidence for safety and effectiveness of the types previously discussed under options for preamendments Class III devices (Option 6).

Postmarketing Monitoring and Controls

The lack of information on risks associated with the use of medical devices can be viewed either as evidence that such risks are not extensive and that more vigorous device regulation is not needed, or instead as an indication that monitoring systems should be improved to yield more information before risks are discounted. Identifying problems is crucial in determining which devices may need additional controls and what types of controls should be applied. Thus, improved information on risks would be helpful both for determining the scope of the problems that regulation could address and in applying the appropriate types of controls.

Option 16: *Require FDA to develop better systems for monitoring and providing information on risks associated with devices.*

FDA is reportedly ready to make final its regulations on mandatory device experience reporting by manufacturers, subject to the Office of Management and Budget's approval (257). GAO has suggested that FDA's voluntary reporting system, the Device Experience Network (DEN), be revised so that information is included on the scope and nature of device problems caused by user error and inadequate maintenance; that the data be analyzed to identify special problems and trends; and that the results be used to aid in developing solutions (331). GAO is also initiating a comprehensive exploration of postmarketing surveillance activities and their potential applications (300).

Thus, there is a gradual movement toward better identification of, and faster and more targeted responses to, device risks. The process might be accelerated by legislating mandatory device experience reporting instead of continuing with the permissive language contained in the statute.

Option 17: Encourage FDA to selectively apply postmarketing controls to regulate Class II devices.

Postarnendments controls could be applied to a new class of Class II devices or left to be applied by FDA on a device-by-device basis (see Options 13, 14, and 15). A reconstituted three-tiered classification approach would result. Minimal regulation would apply to the lowest class of devices through the good manufacturing practices regulations. An intermediate class of devices (Class II) would be represented by those devices that have additional controls (prescriptions, restricted devices, postmarked controls) applied to them of the types identified in addition to the good manufacturing practices requirements. The highest regulated class of devices would have to meet premarket approval requirements and might have additional controls imposed on their marketing.

Assistance to Small Manufacturers

The 1976 amendments contained a provision to help small firms through the regulatory process by establishing an Office of Small Manufacturers Assistance. Two other steps could aid small firms in manufacturing Class III devices: 1) where appropriate, Class III devices could be downclassified as soon as possible; and 2) small firms could be given assistance in developing the safety and effectiveness evidence necessary for Class III device approval.

Option 18: *Develop additional mechanisms to help small firms through the regulatory process.*

Option 18A: Encourage FDA to use publicly available information as soon as possible to down-classify Class III devices.

FDA could take the initiative in identifying Class III devices of significant importance to public health and could monitor their use. Thus, publicly available information could be accumulated at the earliest possible time and down-classification could be initiated.

Option 18B: Develop a "broker" mechanism between small firms with promising devices and clinical investigators capable of performing the tests necessary to gather safety and effectiveness data in support of the premarket approval application for Class III devices.

Although Option 18A might help small firms gain approval for medical devices that are already on the market, it would not help small firms that want to be among the first to have their devices approved for marketing.

There is some precedent for a broker function, although there might be questions of conflict-of-interest if FDA assumed the role. One precedent, for example, is the past and continuing collaboration between commercial sponsors and specific institutes at the National Institutes of Health in performing clinical trials for potentially significant new drugs to meet FDA's requirements of clinical testing for premarket approval. Another precedent is the Federal promotion of "orphan" medical products, in which Federal funds are used to support clinical trials for promising products that have a limited market, such as drugs for rare diseases. Thus, as a broker, FDA could maintain a registry of potentially marketable devices and provide it to interested parties.