This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Threshold Assessment of the
Impact of a Requirements for Submission of Premarket
Approval Applications for 31 Medical Devices
Marketed Prior to May 28, 1976

I. Purpose

The purpose of this threshold assessment is to determine whether a series of regulations, which are expected to result in the submission of premarket approval applications for 31 types of medical devices marketed prior to enactment of the Medical Device Amendments of 1976, have sufficient economic impact to warrant: (1) a regulatory impact analysis under E.O. 12291, or (2) a regulatory flexibility analysis under the Regulatory Flexibility Act (P.L. 96-354).

II. Objective of the Regulations

The Medical Device Amendments of 1976 direct FDA to apply premarket approval requirements to all Class III devices marketed before the amendments (pre-amendments devices). The amendments also authorize the agency to establish priorities in doing so. The purpose of this process is to ensure that these pre-amendments devices are safe and effective for their intended uses.

III. Nature of the Impact

In the FEDERAL REGISTER of September 6, 1983 (48 FR 40272), FDA issued a notice of intent to require premarket approval for thirteen pre-amendments class III devices. The agency has published final rules requiring premarket approval for 7 of those devices and published a proposed rule for 1 more device. Three of those devices are the subject of reclassification petitions and FDA is considering reclassifying those devices. For 2 of the devices, the pacemaker programmers and the implantable pacemaker pulse generator, FDA has implemented the pacemaker registry regulation (52 FR 27756; July 23, 1987) to assure the safety and effectiveness of pacemakers.

In this notice, FDA is announcing its intent to require premarket approval for a group of thirty-one pre-amendments class III devices. Manufacturers of these devices have three general options in responding to this regulation:

(1) They may respond to the proposed rulemaking specified in Section 515(b)(2)A by requesting a change in the classification of the device based on new information.

(2) They may submit a Premarket Approval Application (PMA) to FDA. If they are not ready to do this promptly, they may submit an investigational device exemption (IDE) application in order to conduct further research. This preliminary step would presumably lead to an eventual PMA.

(3) They may cease to manufacture the device if present or future profits from sale of the product do not warrant the additional expenditures associated with preparation of a PMA. This may include situations where the firm concludes it cannot demonstrate safety and effectiveness of the device.

FDA's experience with the first group of 13 devices called for PMA shows that all manufacturers will not choose to submit them. However, because this option is of prime interest in this analysis due to the expectation that it is the most costly option, this threshold analysis will assume that every manufacturer marketing one of these 31 products will prepare a PMA for it.

If the affected manufacturers were developing new post-amendments devices, they would all begin from a comparable starting point, i.e., no experience or test data on the new products. But, pre-amendments devices have quite diverse histories with respect to confirmation of safety and effectiveness, so the cost of investigations required at this point will vary considerably. FDA studied the pre-1976 safety and efficacy testing practices of 27 medical device firms through a series of contract studies.[1] Some firms spent hundreds of thousands of (pre-1976) dollars to test devices, while competitors developing the same device expended comparatively trivial sums. The differences among dissimilar devices is also dramatic. For some, all manufacturers conducted significant testing. For others, testing for safety or efficacy was an exception. From this history, FDA modeled several likely scenarios for individual firms:

Company A pioneered a new type of device 15 years ago and conducted several clinical trials prior to marketing. Since the device amendments were not enacted at the time, the firm conducted these trials to satisfy its own specifications and scientific standards at the time. Efforts to upgrade and improve its product over the past 15 years have prompted Company A to collect and analyze patient data from commercial use of its device at several hospitals. This product, because of its pioneer nature, was also the subject of several research studies published in medical journals. From these sources, Company A has all the data necessary to prepare a PMA. It needs only to assemble the information for submission to FDA.

Company B conducted limited pre-market tests of its first commercial prototype in only 4 patients before introduction 10 years ago. The product evolved quickly. The sixth model, which was implanted in more than 5,000 patients, was very different in design and materials from the first. Company B has closely monitored the post-market experience with Model 6 in order to develop the next generation. From this effort, Company B has most of the data necessary to support a PMA for its Model 6, some of the data necessary for earlier Model's 4 and 5 which it

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1. OPE Study No. 61, Pre-amendment Medical Device Safety and Efficacy Testing, October 1982.

still markets and very little for its earlier versions which are no longer marketed.

Company C is a late entrant in a growing market. Its first product introduced 6 months ago essentially mimics Company B's popular Model 6. Since Company C's product is "substantially equivalent" to pre-amendments devices, it was not required to submit a PMA before marketing. Company C conducted no clinical trials to establish safety and efficacy, but it conducted bench test comparisons with Model 6 which purport to show that Company C's product is superior.

These hypothetical scenarios illustrate some of the variability in impact of these regulations. Company A faces an essentially administrative chore of assembling a PMA from available data. FDA has estimated this cost per year, assuming 600 hours of professional time and 400 hours of clerical time, at approximately $30,000 for a typical PMA submission. Company B needs to decide which of its evolutionary models it wishes to continue marketing and determine the incremental requirements for separate PMAs on the different models. If additional data are necessary, B needs to decide whether it can obtain this information from ongoing commercial use of the product before the deadline for PMA submission, or whether Investigational Device Exemptions (IDEs) will be necessary. Company C faces a situation similar to a new post-amendments device. It has no S&E testing data, and very limited marketing experience. FDA asked 8 firms that had received FDA approval for post-amendment PMAs about their costs for demonstrating safety and efficacy and preparing PMAs. Estimates varied widely from less than $100,000 to $600,000 per year, with an average of about $450,000 per year. Company C will presumably face most of these costs, unless it can obtain information from current commercial users as a basis for a PMA.

The diversity of impacts developed in these scenarios give some idea of the variables that must be considered in developing cost estimates for these regulations. The number of firms, diversity of models, length of market experience, and pre-marketing research practices will all influence costs. The next section will examine these variables in greater detail.

IV. Assessment of Economic Impact

This section considers (1) the number of firms that are likely to submit PMAs for the 31 device types, (2) the average number of different models by each firm, (3) the likelihood that firms will have already developed some of the S&E data, and (4) aggregate cost implications.

Number of Affected Firms and Product Models

The number of firms who will submit PMAs for the 31 devices can be estimated with reasonable confidence from FDA's device listing records and knowledge of current device marketing. Firms who have marketed these 31 devices in the past have presumably listed these devices with FDA, although not all past marketers may currently market such products. Also, some current marketers may not choose to continue marketing the

devices for reasons other than the requirements of these regulations. On the other hand, other new entrants may elect to enter these markets in the near future. Considering these various factors, FDA estimates that about 235 firms may be affected by these regulations. This is an average of slightly less than eight firms for each device type, although some devices may no longer be currently marketed. Approximately ten manufacturers have produced three or more of the device types, about twenty-five manufacturers have produced two of the device types, and the remainder of approximately two hundred manufacturers produce only one of the device types.

A firm may also have different models of a device that require a separate PMA, although substantial portions of the related PMAs may be identical. It is difficult to predict the precise number of substantially different models in current production. The following table estimates the number of firms likely to submit PMAs in the 31 device type categories, and the number of models that may require separate PMAs in each device type.

Device Type	No. of Firms	No. of Models
Immunology and Microbiology Devices		
Herpes simplex virus serological reagents.	39	59
Rubella virus serological reagents.	39	73
Anesthesiology Devices		
Electroanesthesia apparatus.	0	0
Membrane lung for long-term pulmonary support.	6	6
Cardiovascular Devices		
Vascular graft prosthesis of less than 6 millimeters diameter.	5	5
Intra-aortic balloon and control system.	20	58
Dental Devices		
Endosseous implant	59	93
Endodontic dry heat sterilizer.	5	5
Ear, Nose, and Throat Devices		
Endolymphatic shunt tube with valve.	1	1

Device Type	No. of Firms	No. of Models
Gastroenterology-Urology Devices		
Testicular prosthesis.	3	3
Electrohydraulic lithotripter.	15	15
General and Plastic Surgery Devices		
Silicone inflatable breast prosthesis.	17	17
Silicone gel-filled breast prosthesis.	21	32
General Hospital and Personal Use Devices		
Chemical cold pack snakebite kit.	0	0
Neurological Devices		
Cranial electrotherapy stimulator.	5	5
Obstetrical and Gynecological Devices		
Endometrial washer.	4	4
Endoscopic electrocautery and accessories.	2	2
Powered vaginal muscle stimulator for therapeutic use.	2	2
Ophthalmic Devices		
Keratoprosthesis.	1	1
Eye valve implant.	5	5
Orthopedic Devices		
Knee joint femorotibial metallic constrained cemented prosthesis.	4	4
Knee joint patellofemoral polymer/metal semi-constrained cemented prosthesis.	5	5
Knee joint patellofemorotibial plymer/metal/ metal constrained cemented prosthesis.	6	6
Knee joint femoral (hemi-knee) metallic uncemented prosthesis.	3	3

Device Type	No. of Firms	No. of Models
Knee joint patellar (hemi-knee) metallic resurfacing uncemented prosthesis when intended for uses other than treatment of degenerative and posttraumatic patellar arthritis.	8	8
Shoulder joint metal/metal or metal/polymer constrained cemented prosthesis.	1	1
Shoulder joint metal/polymer, non-constrained cemented prosthesis.	7	11
Shoulder joint metal/polymer, semi-constrained cemented prosthesis.	8	12
Shoulder joint glenoid (hemi-shoulder), metallic cemented prosthesis.	3	3
Physical Medicine Devices		
Rigid pneumatic structure orthosis.	0	0
Stair-climbing wheelchair.	6	6
	300	445

Approximately thirty-one percent of the firms began manufacturing one or more of these thirty-one device types ten years or more ago (prior to 1981). Thus, those firms have years of marketing experience, even if they did not conduct pre-market testing. Approximately seventy-seven percent of the manufacturers were marketing their devices prior to 1985. Presumably, many of those firms have utilized the normal commercial use of their products as an economical opportunity to gather S&E data on their products, if not to satisfy the device amendments, then at least to refine and improve their products. Others may have been motivated by FDA's final classification decisions to begin collecting necessary S&E data.

For the preceding reasons, a conservative estimate can be made that at least half of the affected firms are in the situation described for Company A in the preceding section: they need only to assemble available information into a PMA.[2]

2. The sunk costs incurred by manufacturers who initiated testing because of either the enactment of the amendments, FDA's final classification regulations, or anticipation of these requirements are relevant costs for this analysis, but as a practical matter, it is impossible to separate these anticipatory expenditures from normal business costs associated with pre-amendment R&D practices.

For the remaining half, including those manufacturers who may have begun marketing their devices since 1985, it is assumed that their circumstances vary from needing one minor piece of data to Company C's situation of only being slightly better off than a new post-amendments entrant. For this group, we will assume an average incremental R&D effort per year of $200,000, or about half the estimated total cost for a new post-amendment entrant ($450,000 per year).

We made one futher assumption regarding the availability of S&E data for multiple models of a single product. In many cases, variation between models is slight. Hence, additional costs for PMA requirements are minor. In other instances, models are substantially different. To cover the range of possible circumstances, we will assume that each additional model of a firm's device which warrants a distinct PMA requires an expenditure equal to 50 percent of the initial model.

Cost Estimate

The preceding estimates regarding the proportion of firms that may require additional data to submit acceptable PMAs, and the costs associated with acquiring these data, are based on information about pre-1976 industry R&D practices and testing costs for new post-amendments devices. Neither of these conditions precisely match the circumstances of these regulations, i.e., assemblage of S&E data years after marketing of a device, different types of devices. Consequently, these estimates may either overstate or understate actual costs. The Purpose of a threshold assessment, however, is not to calculate precise estimates, but to determine in the simplest fashion possible whether there is a reasonable likelihood of a major cost impact or a substantial impact on a significant number of small firms. The information developed is adequate to make this determination.

The expected cost for the 31 regulations is as follows:

Cost of initial PMA by 50% of firms with all necessary S&E data (150 firms x $30,000)	$ 4,500,000
Cost of initial PMA by 50% of firms needing additional S&E data (150 firms x $200,000)	$30,000,000
Cost of multiple PMAs at 50% rate for initial PMA (145 multiple PMAs x (.50)($115,000)	$ 8,337,500
	$42,837,500

The estimate of $42.8 million is not altered significantly by a change in the assumptions. For example, if instead of 50 percent, only 25 percent of the firms have sufficient S&E data to submit PMAs, the total cost estimate would rise by less than $12.8 million. Similarly, if the cost of a

3. $\$115,000 = \frac{(150 \times \$30,000) + (150 \times \$200,000)}{300}$

PMA for different models was 90 percent of the cost of the initial PMA, total costs would rise about $17.8 million. The agency does not believe these alternative assumptions are realistic, but they do demonstrate that a change in assumptions will not result in costs of a major proportion. Based on experience gained from the previous notice that the agency would call the first group of thirteen devices for premarket approval, it is not likely that the agency would call for all thirty-one of the named devices in one year. Resource constraints on the numbers of applications the agency can review in one year makes this occurrence unrealistic. Thus, this estimate is sufficient for the purposes of a threshold assessment.

Small Business Impact

With regard to the small business impact, the 300 affected firms include about 105 large firms,[4] about 17 foreign firms whose size characteristics are unknown to FDA, and 32 "double counts" (firms who make more than one of the 13 devices). The remaining small firms, numbering about 146 are not a "significant number" in terms of the Regulatory Flexibility Act. Not only is the absolute number small, but based on the previous estimate for the firms manufacturing the first 13 devices called for PMA (which represented less than 0.5 percent of the total medical device firms with less than 100 employees), this group of 146 manufacturers would represent less than 8 percent. Regardless of their number, these small firms are not facing a barrier to market entry in these regulations, or a cost that will likely drive them out of established markets. They are all marketing the affected products—many since before 1976—and are presumably enjoying profits from these products.

Summary

Based on the preceding analysis, the agency concludes that regulations likely to result in the submission of PMAs for 31 types of medical device amendments marketed prior to the Medical Device Amendments of 1976 will not result in a "major cost" under E.O. 12291 or affect "a substantial number" of small firms under the Regultory Flexibility Act.

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4. OPE Study #59, Baseline Data on Medical Device Establishments, September 1981 classified large medical device esetablishments as those with more than 100 employees. They represent about 25 percent of the total establishments in the industry.