7.
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INTRODUCTION

NMR imaging devices are the first imaging devices for which the Food and Drug Administration (FDA) premarket approval has been required under the Medical Device Amendments of 1976. (Previous imaging devices, such as X-ray CT scanners, were introduced before the amendments were passed.) Because the FDA approval process can have such an important effect on the rate at which new technology is introduced into the health care system, it is important to examine how the FDA regulatory process operates and how a promising technology such as NMR imaging has fared in its encounter with it. This chapter is devoted to those two tasks,

The chapter is divided into three sections. The first section describes the statutory sources of FDA authority over NMR imaging devices. The second section describes the process through which new devices such as NMR imagers are brought to market. The section includes a flow diagram (fig. 12) that illustrates the process, and a summary of how NMR imagers have fared in each stage of the approval process. The final section assesses the premarket approval process as a whole and raises a number of policy issues that should be addressed in evaluating it.

SOURCES OF FDA AUTHORITY

Radiation Control for Health and Safety Act

FDA authority over NMR imaging devices derives from two Federal acts. The first is the Radiation Control for Health and Safety Act of 1968, established to protect the public from hazardous radiation emitted by electronic devices. Because no hazards deriving from electromagnetic fields have been identified with current NMR devices, FDA has not established any radiation emission performance standards for NMR devices under the authority of the Radiation Control Act. According to the Director of Electronic Products in FDA's Center for Devices and Radiological Health, ". . . it is not likely that the Radiation Control Act will have any significant impact on the development of NMR imaging as a medical diagnostic modality" (164). However, if defects were found in NMR devices that rendered them unsafe, FDA could use the authority of the act to recall them, even though no performance standards have been developed.

Food, Drug, and Cosmetic Act

The second source of FDA authority over NMR imaging devices is the Food, Drug, and Cosmetic Act as amended in 1976, which controls the introduction of medical devices into commerce. In contrast to the Radiation Control Act, the Food, Drug, and Cosmetic Act has had, and continues to have, a significant impact on the development of NMR imaging devices. The 1976 Medical Device Amendments require that all medical devices intended for human use be classified into three regulatory categories (classes) based on the extent of control necessary to provide reasonable assurance of the safety and effectiveness of each device.

Class I devices are those for which general controls relating to adulteration, misbranding,

banning, notification, reporting, registration, restrictions on sale or distribution, and good manufacturing practices are considered sufficient to provide reasonable assurance of safety and effectiveness.

Class II devices are those for which general controls are considered insufficient to provide reasonable assurance of safety and effectiveness, and for which there is sufficient information to establish a performance standard to provide such assurance.

Class III is reserved for devices: 1) that are used in supporting or sustaining human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury; and 2) for which Class I and Class II controls are either insufficient to provide reasonable assurance of safety and effectiveness or for which insufficient information exists to establish a performance standard that would provide this assurance. Class III devices require premarket approval (PMA) from FDA.

Figure 12 provides a flow diagram that illustrates how a new medical device, such as an NMR imager, finds its way through the FDA process into commercial distribution. The following sections describe the illustrated process in more detail.

REGULATION OF NEW MEDICAL DEVICES UNDER THE FOOD, DRUG, AND COSMETIC ACT

Premarket Notification of Intent To Market a New Device

The Medical Device Amendments of 1976 include a provision titled Premarket Notification (sec. 510(k)), which was designed to ensure that manufacturers did not begin marketing new devices until such devices had either received premarket approval or had been reclassified into Class I or II. Under this provision, a manufacturer must notify the FDA 90 days before it intends to begin marketing a device that was not sold prior to May *28, 1976.* At the time of this Premarket Notification, the manufacturer must also specify the class into which the device has been classified or state the fact that the device has not yet been classified.

Under the 1976 amendments, any new device is automatically classified into Class III unless it is deemed to be "substantially equivalent" to either a preenactment device (i. e., one introduced prior to May 28, 1976) or a postenactment device that has already been classified into either Class I or Class 11. [1]

[1] If the new device is deemed to be "substantially equivalent" to a preenactment device, then the new device automatically assumes the classification of that preenactment device. Of significant importance is the fact that if a new device is deemed to be substantially equivalent to a preenactment Class III device, it may immediately be marketed without a premarket approval application.

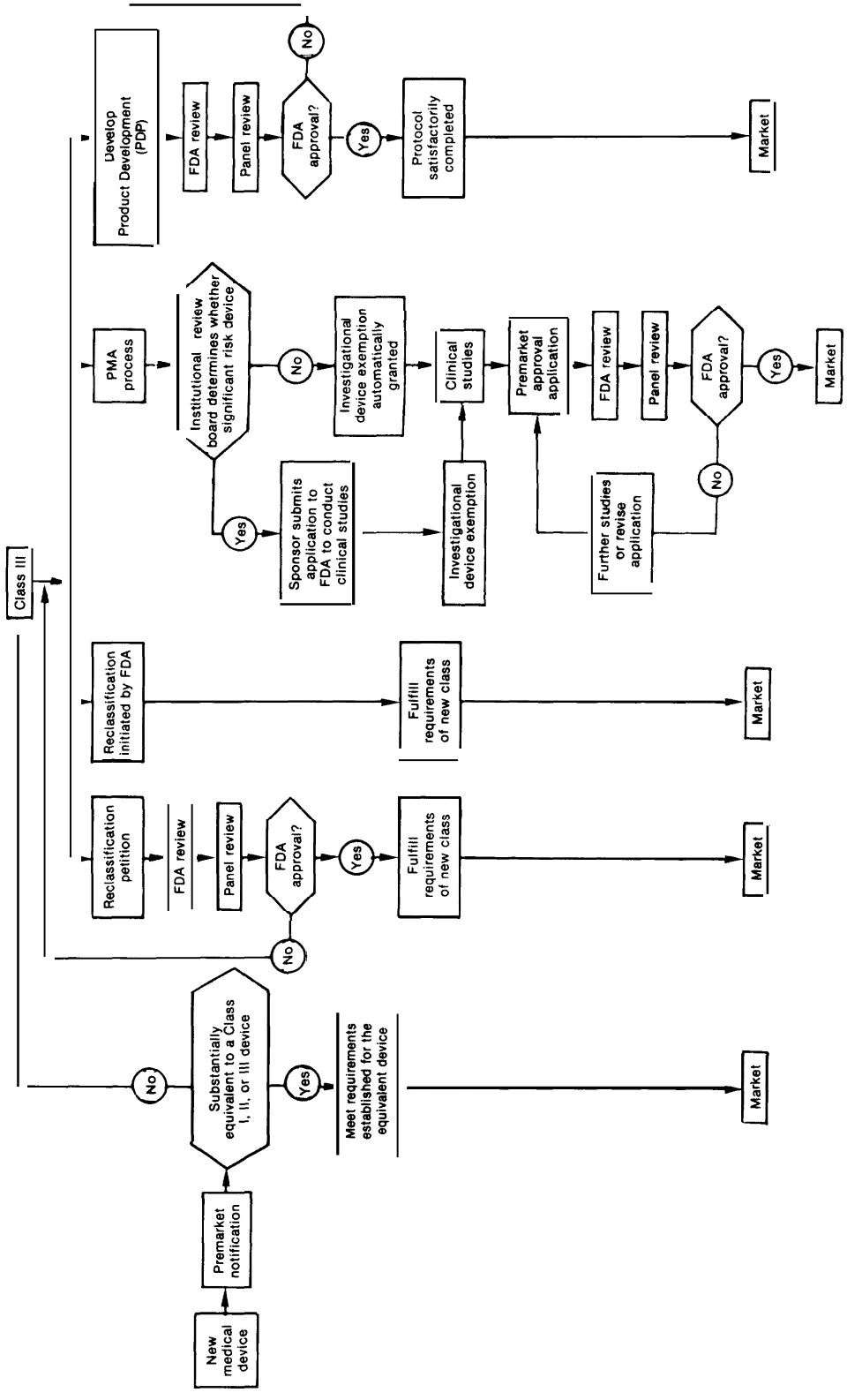
To our knowledge, no NMR imaging manufacturer has submitted a petition to FDA arguing that NMR imaging devices are substantially equivalent to either a preenactment device or a postenactment Class I or Class II device. NMR imaging devices thus are Class III devices that unless reclassified, cannot be marketed prior to approval of a premarket approval application (PMAA) or a Product Development Protocol before marketing (see below).

Getting a Class Ill Device to Market

As indicated in figure 12, a Class III device such as NMR imagers can be brought to market through one of several pathways: reclassification into Class I or II, initiated either by a petition or FDA; premarket approval; or Product Development Protocol.[2] Although NMR manufacturers considered reclassification, they have used the premarket approval approach.

[2] Under a Product Development Protocol, a manufacturer and FDA would agree on a plan of study to demonstrate reasonable assurance of the safety and effectiveness of a device. After receipt of a notice of completion of an approved protocol, FDA may declare the protocol completed or find that the results of the trials performed under the protocol differ substantially from the results required by the protocol, or that the results do not provide reasonable assurance of the safety and effectiveness of the device under the conditions of use in the proposed labeling. At least until December 1983, no manufacturer had elected the approach of a Product Development Protocol.

Figure 12.—How To Get a New Medical Device to Market



SOURCE: E. P. Steinberg, Johns Hopkins Medical Institutions, Baltimore, MD, 1983.

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Reclassification

According to the Medical Device Amendments of 1976, a manufacturer may petition FDA to reclassify a Class III device into either Class I or II. Reclassification petitions are referred to an expert advisory panel that within 90 days must recommend to FDA whether classification of the device in Class 111 is required to provide reasonable assurance of the device's safety and effectiveness. Within 90 days of receipt of the panel's recommendation, FDA must either approve or deny the petition.

On July *6, 1982,* the National Electrical Manufacturers Association (NEMA), a trade association representing 13 companies involved in the development of NMR imaging systems and magnets, requested a meeting with FDA to discuss the possibility of initiating the reclassification process. At a meeting in December 1982, NEMA offered the view that NMR was an anatomical imaging modality whose safety and effectiveness were adequately assured by the General Controls of Class 1. FDA expressed concern that NMR was a rapidly developing technology whose safety and effectiveness had yet to be demonstrated. According to the Director of the Division of Electronic Products in the Center for Devices and Radiological Health:

> The clinical possibilities for NMR imaging and the immaturity of its current applications were factors behind the FDA's opinion that Class III is appropriate for the modality. NMR's promise, while immense, is still unrealized. Clinical experience is still inadequate to establish effectiveness of specific NMR applications and to permit the development of adequate labeling, indications, techniques, and instructions. Each area of research will have to be studied scientifically and clinically to develop this information (164).

The official minutes of the December 8, 1982, meeting state:

> There were a number of concerns that the data presented left a clear impression that industry has not substantiated a general claim that NMR was an effective device that could be utilized across the spectrum as an imaging modality. It was further stated that it would be advisable for industry to start with a limited claim on the effectiveness of NMR with supporting scientific documentation . . . (It was further stated) that the Panel would review **a** reclassification petition if it were submitted in the appropriate legal manner (140).

No reclassification petition had been submitted as of December 1, 1983.

The NMR imager manufacturers that we surveyed were divided over whether it was redundant or wasteful to require that all manufacturers obtain PMA (see below). About half of the manufacturers felt that NMR imaging was sufficiently generic that once a PMAA was approved, FDA should set performance standards rather than continue the PMA requirement for each device. The other half of the manufacturers felt that NMR imaging is not "generic" because important differences exist between available NMR imaging systems, and that, consequently, each manufacturer should be required to obtain PMA (see below), These manufacturers argued in addition that the PMA process serves an important quality-assurance function and should be applied to all manufacturers. Although we think it is important to identify these two viewpoints, we lack sufficient information to comment on either the extent to which different manufacturers' NMR imaging systems do, in fact, differ, or the extent to which manufacturers' opinions reflect, in part, how close they are to obtaining PMA.

The Premarket Approval Process

In order to obtain premarket approval for a device, a manufacturer must provide reasonable assurance that the device is safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling. NMR imaging devices are the first imaging devices to have encountered this process. The following sections explain how the PMA process works and describe how FDA has applied the process to NMR imaging devices.

Significant Risk Devices

A manufacturer may place a device at an investigational site to collect data pertaining to safety

and effectiveness. Such data can be collected according to a plan approved either by a local Institutional Review Board (IRB) (a local committee that reviews proposed scientific studies) or FDA. If the IRB approves the investigation as involving a nonsignificant risk device (one that does not pose serious risk to experimental subjects), the investigation is deemed to have an approved Investigational Device Exemption (IDE) and an application to FDA is not necessary. A sponsor need apply to FDA for approval to conduct clinical studies under an IDE only if an IRB has determined a device to be a "significant risk device, " i.e., a device that presents a potential for serious risk to the health, safety, or welfare of experimental subjects. FDA does not maintain records of nonsignificant risk investigations and may not even be aware that such investigations are being conducted.

On February *25, 1982,* FDA issued "Guidelines for Evaluating Electromagnetic Risks for Trials of Clinical NMR Systems" *(188). The* guidelines were issued by FDA to "provide assistance to sponsors of clinical investigations, researchers, and IRBs in determining when a clinical study involving an NMR device might represent a 'significant risk' under the Investigational Device Exemption . . . and to prevent submission of IDE applications [to FDA] when they are not necessary" (188). The guidelines related to details of NMR imaging that the FDA believed would be least familiar to the IRBs:

> On the basis of current information the bureau believes that a study which does not exceed these guidelines probably does not present an unacceptable risk in these 'three areas:
>
> 1. Static (Direct Current) Magnetic Fields—whole or partial body exposures of 2 tesla (T).
> 2. Time Varying Magnetic Fields—whole or partial body exposures of 3 T/second.
> 3. Radiofrequency Electromagnetic Fields—exposure to RF fields that result in a specific absorption rate that exceeds 0.4 W/kg as averaged over the whole body, or 2 W/kg as averaged over one gram of tissue, Studies that expose patients above these guidelines should be considered to pose "significant risk" (188).

It should be emphasized that in issuing these guidelines, FDA did not declare that NMR imaging was "safe. " Rather, it stated that it was reasonable to proceed with investigations that adhered to these guidelines.

Ten months later in a December 28, 1982, memo to NMR manufacturers, the Director of FDA's Division of Compliance stated that ". . . over the past few months it has become clear that the intention of the guidelines has been widely misunderstood, " and that ". . . it has been rather widely reported to us that the guidelines have been interpreted as limits for patient exposures in NMR imaging investigations . . . This is not our intent" (189).

In an effort to clarify this misunderstanding, FDA stated that:

> It continues to be our view that within the context of the present understanding of the biologic effects of electric and magnetic fields, the medical NMR imaging devices currently in investigational use span a range from those which require no detailed analysis to demonstrate that they do not meet the definition of significant risk to those which do require analysis to make such a determination. It is the purpose of the guidelines to provide some simple criteria for use in establishing that demarcation. No implication should be taken that a device which exceeds the guidelines should necessarily be considered a significant risk device (189).

Our survey of NMR imager manufacturers revealed that most manufacturers found FDA's promulgation of "Significant Risk Guidelines" to have been quite helpful, but expressed two strong concerns. First, although FDA has clearly described its guidelines as an aid to IRBs in making significant risk determinations and not as limits governing patient exposures, simply by virtue of their existence, the guidelines have inevitably tended to become product specifications with which manufacturers are loath not to comply. Second, the manufacturers felt that the FDA guidelines were "poorly conceived. " For example, manufacturers suggested that the 3 T/second guideline pertaining to time-varying magnetic fields was uninterpretable in the absence of a specified pulse duration. (The National Radiologic Protection Board

in Great Britain, for example, suggested a guideline of 20 T/second for pulses more than or equal to 10 millisecond in its 1980 guidelines.)

These two concerns relate more to a disagreement over the content of FDA's guidelines than to their issuance per se. It seems appropriate for FDA to have issued the guidelines. If their content is deficient (and we are not in a position to evaluate that issue), scientific experts could help to change them, and the process through which they were established could be reviewed to assure that it provides for adequate expert scientific input.

Regulations Pertaining to Investigational Devices

During the period in which a device is considered to be investigational (i. e., while it is being assessed under an IDE), manufacturers and investigators must comply with four regulatory prohibitions:

1. they may not engage in promotion or test marketing of the investigational device (21 CFR 812.7(a));
2. they may not commercialize an investigational device by charging the subjects or investigators more for it than the amount necessary to recover costs of manufacture, research, development, and handling (21 CFR 812.7(b));[3]
3. they may not prolong an investigation of a Class III device beyond the point where it has become apparent that premarket approval cannot be justified *(21* CFR 812.7(c)); and
4. they may not represent an investigational device as being safe or effective for the purposes for which it is being investigated (21 CFR 812.7(d)).

In our survey of NMR imager manufacturers, two issues related to IDE regulations were identified. First, a number of manufacturers complained that other manufacturers were not adhering to the spirit of the IDE prohibitions on proapproval promotion and test-marketing of NMR imaging devices. Such behavior, these manufacturers asserted, created **a** situation in which all manufacturers were forced to either test-market and promote, or suffer while following the law. One manufacturer said that to avoid this situation in the future, FDA should limit the number of research sites in which manufacturers are permitted to install investigational devices. In a few instances, such as Neodymium YAG (Yttrium Aluminum Garnet) lasers, FDA has established guidelines for the numbers of patients and the length of followup required in studies of investigational devices (50). Other manufacturers, however, were pleased that FDA was not being more strict in its enforcement activities. They considered the existing situation to be an acceptable compromise between prohibitions and no prohibitions.

The second IDE issue raised by our survey pertains to the prohibition on making a profit from investigational devices. Although manufacturers voiced a preference for being able to make a profit during the IDE stage, most thought the existing prohibition was logical and reasonable in concept.[4] Furthermore, they suggested that, in the case of "high R&D cost" devices such as NMR imagers, it is difficult to recoup R&D expenses during the IDE stage because of the small number installed.

In a recent article, Anthony Young, a Washington, DC, attorney, concurred with the view that the IDE regulations should not present a problem to device manufacturers:

> Existing regulations allow a manufacturer to charge for investigational devices and thus to defray a portion of the expense involved in bring-

[3] According to an undated policy statement issued by the Office of Radiological Health's Division of Compliance, ". . . investigators may charge a patient their normal physician's fee and the cost of scanning the patient, provided the scanning costs do not include a profit. " The letter continues, however, that sec. 50.25(b)(3) of the informed consent regulation requires that "any additional cost to the subject that may result from participation in the research be included in the consent form where appropriate. " FDA agrees that it is appropriate in this situation, since third-part, reimbursement may not occur. (141).

[4] 0ne manufacturer felt that the existing prohibition on profitmaking from proapproval devices disproportionatel, hurt small manufacturers. Small manufacturers, it was argued, generally are dependent on external sources of capital to fund research and development and do not fare well in their quest for funds when they are prohibited from demonstrating a profit. Others argued, in contrast, that what is required for success in external capital markets is profitmaking potential, rather than profits themselves. It would seem that without the prohibition on profitmaking during the IDE stage manufacturers would have less incentive to apply for PMA.

ing a new device to market. There is sufficient latitude in the regulations concerning publicity of availability of the device that the manufacturer can reach those practitioners who will eventually become customers. A manufacturer who is straightforward in his claims for his device and who does not attempt to circumvent regulations in an attempt to get a jump on competitors should have no problems with FDA (206).[5]

Clinical Studies

With an IDE in hand, manufacturers may conduct clinical studies to substantiate the safety and effectiveness of the devices they propose to market, Under Federal regulations, well-controlled investigations are the principal means used to establish the effectiveness of a device. However, according to the committee report accompanying the Medical Device Amendments, FDA is authorized to accept meaningful data developed under procedures less rigorous than well-controlled investigations when well-documented case histories assure protection of the public health or when well-controlled investigations would present undue risks for subjects or patients. This provision is not intended to authorize approval on the basis of anecdotal medical experience with the device or unsubstantiated opinion as proof of effectiveness (183).

During the proapproval period, FDA realized that manufacturers were concerned about how to establish the safety of NMR. FDA responded to this concern by exempting manufacturers from responsibility for submitting data on electromagnetic interactions in their PMA applications. FDA's actions and rationale were summarized by Mr. Schneider of the Center for Devices and Radiological Health:

> After considering the biological interactions of the fields used in NMR imaging, [FDA] concluded that the existing fundamental scientific uncertainties could not be resolved by experiments normally associated with device evaluation.
>
> In fact, it would probably be economically impractical for any individual sponsor to assume the financial burden of supporting the research necessary to make significant progress in eliminating these uncertainties. Further, it would seem unwise, with respect to societal benefits, to suspend the development and deployment of NMR imaging as a medical diagnostic modality pending substantial improvement in the understanding of the biological interactions of radiofrequency electromagnetic fields and static magnetic fields.
>
> From available information, no immediate acute effects are expected from exposure conditions prevailing in the devices under investigation. Further, it seems that whatever risks maybe associated with these exposures will be small compared to the potential medical benefits of the modality. [Therefore], potential sponsors have been advised that they need not submit experimental data on electromagnetic biological interactions as part of the safety component of a premarket approval application. Each sponsor was asked to provide an assessment of the physical exposure conditions in its device. The FDA will conduct a continuing review of the risk potential of these exposures in light of developing scientific knowledge (164).

The Premarket Approval Application

When a manufacturer believes it has collected sufficient data to establish the safety and effectiveness of its device, it submits a premarket approval application (PMAA) to FDA. The PMAA must include:

1. a statement of the components of the device;
2. a statement of the principles of operation of the device;
3. a description of the methods used in the manufacture of the device;
4. a summary of investigations and information bearing on the safety and effectiveness of the device under the proposed conditions of use; and
5. specification of the claims, indications, and instructions with which the manufacturer proposes to label the device.

The type and breadth of the claims made in the proposed device label determine, in part, the scope of the research that must be performed prior to submission of a PMAA. As Schneider of FDA explains:

> Each claim that is made must be supported by adequate scientific and clinical research. This means that in broadening the range of claims for

[5]Mr. Young's statement should in no way be construed as representative of FDA's viewpoint.

> a device, a sponsor increases the expense and effort necessary to secure premarket approval (164).

With regard to NMR, Schneider has stated that:

> . . . there is a natural temptation to be enthusiastic about all possible applications of the modality. Under the premarket approval process, this can be expensive when a device is as new as NMR imaging . . . Under these circumstances, a sponsor may wish to make claims that insure commercial viability of a system but that are not inordinately costly (164).

In November 1980, FDA published a "Guideline for the Arrangement and Content of a Premarket Approval Application" to aid sponsors in the preparation of such applications (187). According to those guidelines, a PMA application should include a description of the disease(s) or condition(s) that the device will diagnose and the patient population for whom the device is intended.

About half of the manufacturers surveyed stated that they would have liked more precise guidelines from FDA regarding the required content for a PMAA (e.g., how many patients need to be studied, whether studies need to be blinded, etc.); the others felt that sufficient guidance had been provided by FDA. Manufacturers who had received feedback from FDA on submitted PMAAs felt that FDA officials had been extremely helpful, fair, and reasonable in their review of PMAAs, particularly since NMR was the first Class 111 imaging device to go through the PMA process. A fairly common complaint from manufacturers, however, was that the PMAA format was unnecessarily tedious and complicated.

FDA Review

FDA is allotted 180 days to review and either approve or disapprove a PMAA that *satisfies all regulatory requirements.* During this review process, FDA customarily provides feedback to sponsors regarding possible deficiencies in their PMAAs. The underlined qualifier can thus take on significant importance, since FDA can stop the 180-day clock while a sponsor responds to or remedies the possible deficiencies that have been identified by FDA.

Panel Review

The Medical Device Amendments require that FDA refer each PMAA to an appropriate expert advisory panel which, after considering all data provided, makes a *nonbinding* recommendation to FDA regarding whether the PMAA at issue should be disapproved, approved, subject to certain modifications, or approved. On July *6* and *7, 1983,* FDA conducted an open hearing of the Radiologic Devices Panel on three NMR device PMAAs submitted by Diasonics, Picker International, and Technicare. Picker's PMAA pertained to NMR imaging of the head and neck only, while Diasonics' and Technicare's pertained to NMR imaging of both the head and body, The panel considered all the applications "approvable" and voted unanimously to recommend approval of all three PMAAs, subject to various contingencies, such as making specified modifications in Site Planning Guides or labeling.

FDA Approval

The Medical Device Amendments state that a PMAA is to be denied if:

1. reasonable assurance is lacking that the device is both safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling;
2. the methods used in the manufacture of the device do not conform to Good Manufacturing Practices;
3. the proposed labeling is false or misleading in any particular; or
4. the device does not conform to a performance standard with which it is to comply.

In evaluating the safety and effectiveness of a device for PMA of a Class III device, FDA considers, among other relevant factors:

1. the persons for whom the device is represented or intended;
2. the conditions of use for the device, including conditions prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. the probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and
4. the reliability of the device (21 CFR 860.7).

After having considered these factors, FDA regulations specify that:

1. *There is reasonable assurance that a device is safe when* it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use (21 CFR 860.7).
2. *There is reasonable assurance that a device is effective when* it can be determined, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results (21 CFR 860.7).

The safety and effectiveness of a device must thus be considered in conjunction with one another, since assurance of safety depends on an evaluation of effectiveness.

FDA issued formal premarket approval for NMR imaging devices manufactured by Diasonics and Technicare on March **30, 1984,** and for head and neck imaging devices by Picker on May 10, 1984.

CONCLUSIONS: THE PMA PROCESS AS A WHOLE

The application of the PMA process to NMR imaging devices raises several issues. First is whether there should be a PMA process at all, and, if so, what benefits derive from it. Congress established the PMA process in 1976 in response to a perceived need for greater protection from unsafe, unproven, ineffective, and experimental medical devices. At least with regard to NMR imagers, the PMA process seems to have successfully addressed that perceived need. Although disagreements may exist over how much data should be required before PMA is granted, there seems to be a general consensus that the PMA process serves a useful function in assuring the safety and effectiveness of marketed devices. As one manufacturer stated, "The PMA process provides the discipline required to force manufacturers to develop information they ought to have. "

The second general PMA issue relates to whether a separate PMA should be required for each clinical application of NMR or whether PMA should be granted for the technology as a whole. No clear consensus emerges on this issue. On the one hand, it seems possible that an imaging technology such as NMR may well prove to be effective in some but not all potential applications, suggesting that it would be reasonable for FDA to grant PMA on a clinical application, by clinical application basis, much as it does with drugs. On the other hand, it can be argued that as long as there is reasonable assurance that NMR imaging is safe and that NMR is effective, in the sense that it gives a fairly accurate representation of internal anatomy, pathology, or function, it should be up to physicians, rather than FDA, to decide which NMR applications are appropriate. Given some threshold level of demonstrated effectiveness, it would seem that the latter viewpoint is not only reasonable, but also may be the only feasible one for FDA to adopt, since FDA cannot control each application once NMR devices are installed. [b] How FDA resolves this issue may depend on the breadth of the claims made by manufacturers in their proposed labels,

[b] Although it would not be feasible for FDA itself to enforce a restriction on the use of NMR to certain clinical applications, the absence of third-party coverage for uses not approved by FDA might effectively curtail such uses.

A third general issue relates to the manufacturers' costs for data collection and PMAA preparation and FDA's costs for reviewing the applications. The central question regarding the cost of the PMA process for the manufacturer relates to the amount of money that would not otherwise have been spent on the assessment of safety and effectiveness if the PMA process did not exist. Most manufacturers said the difference was "a negligible amount, " with most of it associated with employment of study design consultants and clerical preparation of the PMAA itself. FDA estimated that by July 1983 it had expended about 800 person-hours of effort on reviewing the first three NMR PMAs submitted to it (163). These estimates do not suggest that FDA regulation of NMR devices has entailed high direct costs. To the extent that these assessments are accurate, there seems to be little at issue other than the possibility of streamlining the PMAA itself. To the extent that pertinent, well-designed clinical studies are performed that would not otherwise be funded by manufacturers in the absence of the PMA process, it would seem that the PMA process is serving a useful function.

Fourth, the question arises as to how much the PMA process has constrained development and early placement of NMR imagers. There is no indication that the PMA process has restrained development of the prototypes themselves. In addition, the great majority of NMR manufacturers that we surveyed in the summer of 1983, stated that if the PMA process had not existed, they would have placed few, if any more NMR imaging systems in hospitals than they had already because many manufacturers were still developing and refining prototype systems and had not yet begun full "assembly-line" production capable of meeting existing demand. FDA thus does not appear to be significantly delaying the introduction of experimental model NMR imaging devices into hospitals. In addition, it should be realized that manufacturers use the experience they gain during the IDE period to refine system designs before embarking on full-scale production.

The actual and potential impact of the PMA process may well change in the near future, however, as manufacturers emerge from the prototype development stage. Manufacturers have stated, for example, that many existing "orders" are contingent on the manufacturers' receiving PMA. If PMA is not granted in a timely fashion, these manufacturers may begin to experience delays in receiving revenues to cover their development costs.

Perhaps the greatest potential impact of the PMA process—stemming from its ability to confer a competitive advantage on manufacturers who have received PMA first—is yet to be seen. How much of a financial benefit, in both the short and long run, will accrue to NMR manufacturers who are first to obtain PMA may well help determine not only the future of the NMR manufacturing industry, but also the speed with which manufacturers pursue development of other new technologies that emerge in the future.