Public Health Effectiveness of the FDA 510(k) Clearance Process: Balancing Patient Safety and Innovation: Workshop Report

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Theresa Wizemann, Editor; Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process; Institute of Medicine

PUBLIC HEALTH EFFECTIVENESS OF THE FDA 510(k) CLEARANCE PROCESS

Balancing Patient Safety and Innovation

Workshop Report

Theresa Wizemann, *Editor*

Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process

Board on Population Health and Public Health Practice

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards of objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We thank the following for their review of this report:

Robert J. Genco, State University of New York at Buffalo
Theodore S. Lawrence, University of Michigan Medical School
John H. Linehan, Northwestern University
Patricia B. Shrader, Becton, Dickinson and Company

Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of this report before its release. The review of the report was overseen by **Enriqueta C. Bond,** Burroughs Wellcome Fund. Appointed by the Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests with the authors and the institution.

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Abbreviations

CDRH	Center for Devices and Radiological Health (FDA)
CE Mark	European Conformity mark
CHMP	Committee for Human Medicinal Products
CLIA	Clinical Laboratory Improvement Amendments
EMA	European Medicines Agency (formerly EMEA)
FDA	US Food and Drug Administration
FDAMA	FDA Modernization Act
FFDCA	Federal Food, Drug, and Cosmetic Act
GHTF	Global Harmonization Task Force
GMP	good manufacturing practice
GRAE	generally recognized as effective
GRAS	generally recognized as safe
HDE	humanitarian device exemption
IDE	investigational device exemption
IFU	instructions for use
ISO	International Organization for Standardization
IVD	in vitro diagnostic
LBT	lab-based tests

MDA	Medical Device Amendments of 1976
MDR	medical device reporting
NDA	new drug application
NSE	not substantially equivalent
PMA	premarket approval
QSR	quality systems regulation
TPLC	total product life cycle

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Introduction[1]

At the request of the Food and Drug Administration (FDA), the Institute of Medicine (IOM) has convened a consensus committee to review the 510(k) clearance process for medical devices.[2] Also known as premarket notification, the process in Section 510(k) of the Federal Food, Drug, and Cosmetic Act requires a manufacturer of medical devices to notify FDA of its intent to market a medical device at least 90 days in advance. That window of time allows FDA to evaluate whether the device is substantially equivalent to a product already on the market, in which case the device does not need to go through the premarket approval process. The current 510(k) process, as written in statute and implemented by FDA, is intended to meet two primary goals: (1) to make safe and effective devices available to consumers and (2) to promote innovation in the medical device industry. Concern has been raised, however, that the 510(k) process permits inadequately tested devices to reach the market and thereby places the health of patients at risk. There are also concerns that there is a lack of predictability, consistency, and transparency in the process, potentially inhibiting innovation.

The IOM Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process will assess whether the 510(k) clearance process

[1]The report summarizes the views expressed by workshop participants, and while the committee is responsible for the overall quality and accuracy of the report as a record of what transpired at the workshop, the views contained in the report are not necessarily those of the committee.

[2]Further information about the committee is available at http://www.iom.edu/Activities/PublicHealth/510kProcess.aspx.

optimally protects patients and promotes innovation in support of public health and, if not, what legislative, regulatory, or administrative changes are recommended to achieve the goals of the 510(k) process. The committee is assembling materials that it will examine and discuss in developing its findings, conclusions, and recommendations. A final consensus report is expected to be released in the middle of 2011.

As part of its fact-finding process, the committee held the first of two public workshops on June 14–15, 2010, in Washington, DC, to gather information relevant to the statement of task. David Challoner, chair of the Institute of Medicine's Committee on the Public Health Effectiveness of the FDA's 510(k) Clearance Process, reminded participants that the committee has, as yet, made no conclusions, and that comments made by individuals, including members of the committee, should not be interpreted as positions of the committee or the IOM. In addition, committee members typically ask probing questions in IOM information-gathering sessions that may not be indicative of their personal views.

The following chapters summarize the presentations and panel discussions that occurred in the workshop. Chapter 2 provides an overview of the legislative history of the Medical Device Amendments of 1976, which instituted the 510(k) process. Chapter 3 focuses on FDA's regulation of medical devices. A commissioned paper (Appendix C) on the premarket notification process, written by two former FDA Center for Devices and Radiological Health (CDRH) staff, was presented by one of its authors, and FDA's compliance infrastructure was discussed by the current director of the CDRH Office of Compliance. The commercial medical device industry is the subject of Chapter 4. The structure of the industry's innovation ecosystem was explained, and a second commissioned paper (Appendix D), on the impact of the regulatory framework on device innovation, was presented by its author, a former director of CDRH. After the presentations, a panel discussion expanded on the topic of balancing patient safety and innovation. The presentations and panel discussion in Chapter 5 offer a picture of the global regulatory environment of medical devices, including efforts toward global harmonization. Finally, as part of the committee's fact-finding process, participants were offered the opportunity to make 5-minute statements on issues relevant to the committee's task. Highlights of the public comments are presented in Chapter 6. The workshop agenda and biographic sketches of the speakers are in Appendixes A and B, respectively.

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Legislative History of the Medical Device Amendments of 1976

Peter Barton Hutt, senior counsel to the Washington, DC, law firm of Covington & Burling and former chief counsel (1971–1975) to the Food and Drug Administration (FDA), provided the committee with an overview of the legislative history of the Medical Device Amendments of 1976 (MDA).

An inherent problem in a statute that requires premarket approval (PMA) is how to handle products that are already on the market on the date of enactment. Should the new requirements be imposed on the products already on the market, or should such products be given grandfather status?

There were three precedents to consider in drafting of the 1976 amendments, Hutt said. The Food Additive Amendments of 1958 stated that all food additives on the market on the date of enactment had 3 years, until 1961, to obtain FDA approval. That was unrealistic for both industry and FDA to comply with, Hutt noted. The FDA of the late 1950s was a small organization with a budget of less than $70 million. Congress ultimately had to pass two additional laws to extend the time. But it was clear that a model of that type was not appropriate for drafting the MDA. The second precedent was the Color Additive Amendments of 1960, which gave industry 2.5 years to get approval for their color additives that were already on the market but allowed FDA to extend that time without limit. There are still color additives on the market that have not been approved. Giving extensions in perpetuity did not appear to be a workable solution to the problem. Finally, the Drug Amendments of 1962 mandated that a new drug be proved effective as well as safe to gain approval. Drugs that were on the market before the amendment either were grandfathered (that is, considered

not to be new drugs that needed approval) or could remain on the market until FDA reviewed them and made decisions about their efficacy. FDA had to review 8,000 new drug applications for pre-1962 drugs. Now, 48 years later, there are still 20 products whose status has not yet been resolved.

On May 13, 1962, President Kennedy introduced two pieces of legislation in Congress: one that ultimately became the Drug Amendments of 1962 and one that dealt with new device applications and new cosmetic applications. The device legislation essentially applied the entire system of new-drug regulation to medical devices. Any device that was generally recognized as safe (GRAS) and generally recognized as effective (GRAE) was exempted. The bill provided 18 months, which FDA could extend to 30 months, for all pre-existing devices to be approved. That approach was unworkable, Hutt said, and would have been similar to the food additive approach in which neither industry nor FDA could realistically comply with the timelines. Needing to respond to the thalidomide disaster, however, Congress focused only on passage of the drug bill and said that it would enact medical device legislation in the following year. It took 14 more years to enact medical device legislation.

From 1962 to 1969, every president of the United States, in major addresses to Congress, endorsed medical device legislation. Bills were introduced with every kind of approach to the question of preamendment devices on the market and postamendment medical devices coming onto the market, but none of the bills came close to enactment, Hutt said.

In 1969, the Supreme Court issued a decision in the *Bacto-Unidisk Company* case that said that an antibiotic-sensitivity disc (a laboratory tool used to determine whether cultures of bacteria are sensitive to particular antibiotics—a product that does not ever touch the human body) was a drug. The Supreme Court decision stated that FDA did not have adequate device legislation and so the Court was expanding the concept of a drug so that the agency could require new drug applications for diagnostic products and other important medical items.

That meant either that FDA was going to go forward and designate whatever devices it deemed necessary as drugs or that Congress needed to approve new device legislation. President Nixon, in a message to Congress, ordered that the matter be reviewed by a committee to be established by the Department of Health, Education, and Welfare. Ted Cooper, who was the director of what is now the National Heart, Lung, and Blood Institute of the National Institutes of Health, was chosen to chair the committee. In September 1970, the "Cooper Committee report" was issued. It recommended creation of three classes of medical devices on the basis of the amount of regulation necessary for each class; the first class would be exempt from standards or premarket clearance (subject only to general controls), the second would require controls through the use of standards, and the third

would be subject to performance review (similar to what is now referred to as PMA). The report did not address how to apply the new requirements to products that were already on the market, but it unequivocally established the proposition that devices, which are continually modified, are not drugs. Although it was not called this at the time, it was a risk-based statute that assigned devices to high-risk, medium-risk, and low-risk categories.

In 1970–1976, the Senate Committee on Labor and Public Welfare, chaired by Edward M. Kennedy, introduced medical device legislation and twice passed it. The Senate bill had a provision that would have required PMA only when FDA issued a regulation. It solved the problem of preamendment and postamendment devices by saying that no manufacturer had to seek PMA for a device until every device in the same class of device had to be approved. If a device was already on the market, the manufacturer would have up to 5 years to get a PMA application approved. Again, the hard deadline of 5 years was of concern in light of how few resources FDA had to meet the deadline. In addition, the provision granted a 5-year monopoly to preamendment devices.

Legislation was introduced in 1971 and again in 1973 by Harley Staggers, chairman of the House Interstate and Foreign Commerce Committee. Among its deficiencies, it did not provide for FDA taking an inventory of all devices and did not provide for classification of devices.

The Health Subcommittee of the House Committee on Interstate and Foreign Commerce, chaired by Paul G. Rogers, drafted and introduced a bill 1 month after the Cooper Committee report was released in 1970 and then drafted and introduced bills in 1971, 1973, 1975, and 1976. The initial House bills of 1970 and 1971 defined class I as everything that was GRAS and GRAE. The use of GRAS and GRAE were of concern because as a result of their inclusion in the 1958 Food Additive Amendments and the 1962 Drug Amendments, companies went ahead and marketed their products as safe and effective, and then FDA would have to bring legal action in the courts to take them off the market. Class II at that time was subject to standards (now called special controls) that applied to both preamendment and postamendment devices. Class II was essentially a buffer, a place for devices that are halfway between those requiring general controls and those requiring PMA. For Class III, the House bill was comparable with the Senate bill, giving manufacturers of preamendment devices 30 months, which could be extended to 60 months, to get PMA.

Later, Hutt (then chief counsel for FDA), Charles Edwards, and Alexander Schmidt established an inventory of some 8,000 devices that were on the market, set up classification panels, and established the Bureau of Medical Devices in FDA. Those technically unauthorized actions drew the attention of the House, as intended. David Meade, of the Office of Legislative Counsel in the House of Representatives; Steve Lawton, assistant to

Paul Rogers for food and drug law matters; Rod Munsey, representing the Pharmaceutical Manufacturers Association; and Hutt, representing FDA, then spent 2 months totally rewriting the statute. At the time, Hutt noted, 13 trade associations represented the medical device industry and requested an opportunity for input; these ultimately assembled into what is now the Advanced Medical Technology Association, or AdvaMed.

In the draft that would become the MDA, the issue of classification was separated from the issue of how a device gets to market. Hutt noted that calling this the 510(k) process is something of a misnomer in that it is actually Section 513 of the Federal Food, Drug, and Cosmetic Act that requires FDA to classify medical devices as class I, II, or III on the basis of potential risks and benefits. Section 510(k) was written as a reporting obligation. FDA had no authority to approve a 510(k) submission. Until 1990, when the law was changed, a manufacturer merely submitted a 510(k) report to FDA and placed its product on the market. The original objective was for FDA to have knowledge of all devices on the market so the Agency could prioritize and determine the appropriate classification and requirements.

The legislation stated that a postamendment device could be marketed if it was not "significantly different" from an existing device. There were no deadlines in the standard provisions for devices that needed to be approved and no time limit for FDA to review preamendment devices. That gave discretion to FDA throughout the statute by using general terms. A banned-device provision was included to ensure FDA's authority to put a notice in the *Federal Register* and remove a product from the market. There is adequate authority for FDA to require reports from the industry about adverse events resulting from use of their devices. (In response to a committee question, Hutt added that although it was not feasible then, it would be realistic now to set up a broad national system that would link databases of institutions that use medical devices.) The drafters' intent was that FDA would actively set priorities and potentially revise what was considered a reasonable model for substantial equivalence as it went along rather than necessarily becoming passive and allowing things to continue with no end in sight.

After the bill was introduced in March 1973, it was decided that *not significantly different* was not ideal, and *substantially equivalent* was included in the final legislation. The MDA was enacted in 1976.

3

Premarket Notification

PREMARKET NOTIFICATION AS A KEY ELEMENT OF US REGULATION OF MEDICAL DEVICES

To gain a foundation on which to build its discussions, the committee commissioned two former Center for Devices and Radiological Health (CDRH) staff to draft a background paper on the 510(k) or premarket notification process, explaining the concept of substantial equivalence and discussing the scientific integrity of the process, its strengths, its weaknesses, and its flexibilities.[1] Coauthor Philip J. Phillips, of the Phillips Consulting Group and formerly the deputy director for science and regulatory policy at CDRH, presented an overview of the paper that he drafted in collaboration with Larry Kessler, of the University of Washington School of Public Health, who previously served as director of the CDRH Office of Science and Engineering Laboratories and director of the CDRH Office of Surveillance and Biometrics.

Breadth of FDA Responsibility

FDA regulates a complex and broad array of medical devices and device-related products. The agency has authority over general-purpose articles, such as glassware and reagents, that are used in laboratories; although these are not labeled specifically for medical purposes, their use is medical. FDA regulates device components and parts and the accessories that go with them. Even cases for holding spectacles and contact lenses technically are medical devices. Some devices are custom-built to meet the specific needs of

[1]The complete commissioned paper is available as Appendix C.

an individual patient or an individual health-care practitioner. A new industry that has emerged in the United States reprocesses single-use disposable devices and reintroduces them into interstate commerce as new, and these are subject to the same FDA regulatory review processes as the original devices. Similarly, there is an industry that remanufactures durable medical equipment, including some class III medical devices, and reintroduces them into interstate commerce.

The system of identifying generic types of devices and classifying them is critical for the successful regulation of such diverse products. It is an efficient means for the agency to allocate its resources and maximize FDA's effect on public health.

Safety and Effectiveness

The same definitions of safety and effectiveness apply to all medical devices, whether they are in class I, class II, or class III. How safety and effectiveness are determined is outlined by statute and regulation. Factors that are taken into consideration include the intended patient population, the conditions of use that are communicated through labeling and advertising, the balance of health benefits and risks associated with use of a device, and the reliability of the device.

For FDA to allow a product to be marketed in the United States, there must be

- **Reasonable assurance of safety.** The probable benefits derived from the use of the product must outweigh the probable risks; there must be an absence of unreasonable risk of illness or injury associated with the use of the product.
- **Reasonable assurance of effectiveness.** Use of the product must yield clinically significant results in a significant portion of the target population.

Device Classification

The approach to ensuring safety and effectiveness depends heavily on a device's classification. Class I devices are subject to general controls, class II to special controls, and class III to premarket approval.

Phillips pointed out that premarket notification is the general control that gives the agency an opportunity to determine whether a new product falls into an existing generic type of device or should be considered as a different generic type (it could be in class III, or it could be the subject of a de novo or reclassification effort and be in class I or class II).

Generic type of device is defined by regulation and means a group of

devices that do not differ substantially in purpose, design, materials, energy sources, function, or any other feature related to safety and effectiveness. The agency must conclude that similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness. If a new device is put into class I in accordance with an existing regulation, the general controls applicable to that generic type of device ensure its safety and effectiveness. If a device is put into class II, the general controls *and* the applicable special controls that have been developed ensure the product's safety and effectiveness. More than 1,800 generic types of devices are the subjects of classification regulations.

Premarket Notification

In the early days, the initial 510(k) submissions were simple to review, Phillips said, because there were no substantial differences between new devices going to market and older devices that had been on the market. However, the challenges associated with substantial equivalence quickly emerged. There was an expectation at the time that the Bureau of Medical Devices would start to develop performance standards for class II medical devices, but FDA did not have the resources to do it. Differences between new devices and old devices rapidly became more pronounced, and there were changes that would affect the intended use of a device and technologic changes. Another factor that challenged the system was that any kind of substantial shift toward using the premarket approval (PMA) process more frequently would seriously drain FDA resources. The PMA process was so burdensome and demanding that there was pressure in the agency to bolster the concept of substantial equivalence, which would allow products to go to market quickly with appropriate safeguards. Substantial equivalence evolved to compensate for regulatory realities.

A device is "substantially equivalent" to a predicate device if it has either of the following two groups of characteristics.

It

- has the same intended use as the predicate *and*
- has the same technologic characteristics as the predicate.

It

- has the same intended use as the predicate, *and*
- has different technologic characteristics, and the information submitted to the agency does not raise new questions of safety and effectiveness, *and*

- is demonstrated to be at least as safe and effective as the legally marketed device.

Intended use, as defined by regulation (21 CFR 801.4), refers to the intent of persons legally responsible for the labeling. However, this particular definition is not geared to the premarket determination of intended use. It is a postmarket regulation that gives FDA the authority to determine whether someone is distributing a product and promoting it in a way that is consistent with what FDA views as its legal intended use. In the context of a 510(k) submission, when FDA considers issues of intended use, it focuses primarily on indications for use, on whether a product is intended for use by licensed health-care practitioners or laypersons, and on whether the product is intended for single or multiple use. Changes in the indications for use present the biggest regulatory challenges, and the related agency decisions can be the most difficult to explain.

Indications for use is not defined specifically within the confines of 510(k). For PMA, it refers to the disease or condition that a product is used for and the patient population for which the product is intended. For 510(k) devices, indications for use may be functional (that is, what the device does). In the case of very simple devices, such as scalpels, it is not necessary to name all the patient populations or all the diseases and conditions in which the devices may be used. It is not reasonable to describe use to that level.

Two basic changes in indications for use appear in labeling. One is expansion of the patient population. For example, cardiovascular diagnostic catheters may be proposed for use in cardiac ablation procedures. In that case, a cardiovascular mapping catheter that is used for diagnosis is a class II medical device, but the same product promoted and labeled for therapeutic purposes is a class III device subject to PMA requirements.

The other is a change from general to specific indications for use and vice versa. For example, carbon dioxide lasers, which are very old devices that have not changed much from a technologic standpoint, have had considerable changes in indications for use over the years. Carbon dioxide lasers that are labeled for such procedures as photocoagulation, cutting, and ablation of soft tissue are now being proposed specifically for the removal of tattoos. A guidance document available for general and specific intended uses, Phillips noted, outlines the criteria that FDA uses in making a decision about intended use.[2]

Phillips suggested that the IOM committee consider the following definition to understand FDA's 510(k) approach to intended use:

[2]Guidance is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm.

> In the context of 510(k), intended use is a regulatory concept that determines the boundaries of use for a generic type of device, and is constructed to encompass the widest breadth of use where the regulatory controls for the device type continue to ensure safety and effectiveness.

According to the statute, in the face of different technologic characteristics, the agency asks whether the differences raise new safety or effectiveness questions. If the answer is yes, the device is found to be not substantially equivalent. The agency has not applied the statutory language exactly but asks whether the new technology raises new *types* of questions about safety and effectiveness. The reason that that word *types* was added to the program guidance is that any change in technology can raise a new question. By asking about new types of questions, the agency has greater discretion in making some of its regulatory decisions, Phillips said. Similarly, when considering whether a product is as safe and as effective as another product, the agency asks whether the risks that are inherent in the new technology can be mitigated. In other words, if the technology and the effect of the change on the actual use of the product are well understood, the agency does not automatically reclassify the device to make it subject to PMA; instead, it looks to mitigate risks.

An example is wireless technology. During the last 15–20 years, many devices have been updated to function through wireless mechanisms. Rather than reassess every device, the agency provided requirements for performance testing and labeling to ensure that the risks associated with each wireless-technology device had been mitigated.

Scientific Integrity of the 510(k) Process

Regardless of a common misperception, a 510(k) submission always contains data, Phillips said. The manufacturer of a product that has the same intended use and the same technologic characteristics as a predicate device must submit descriptive data, including side-by-side comparisons of the new device and the legally marketed device with which it is compared, and performance data when descriptive data do not ensure performance. If there are differences in intended use between a new device and a predicate that do not constitute a "new intended use" and there are different technological characteristics, the submission will contain descriptive and performance data, as well as bench, animal, and clinical data to assess those differences and mitigate any associated risks.

The 510(k) process is not only for new manufacturers and new devices that are coming to market, Phillips said. It also applies to existing manufacturers that are modifying their already-marketed devices. Change is inevitable. Whenever there is a change that could substantially affect safety

and effectiveness, the manufacturer must obtain a new clearance from FDA before it can introduce the product into commercial distribution. It is the manufacturer's responsibility to know when modifications and changes require submission of a 510(k), and there is FDA guidance for industry in addressing this.[3]

Ultimately, the integrity of the 510(k) process requires verifying that FDA is receiving the necessary submissions and that in all cases the changes have undergone the necessary verification and validation.

Strengths, Weaknesses, and Flexibilities

A key strength of the 510(k) process is FDA's ability to apply knowledge that has been gained in the review of one 510(k) submission to the review of later 510(k) submissions. That does not mean that confidential, proprietary information is shared externally. Rather, the agency can use it internally so that it does not have to ask redundant questions.

A weakness in the program is the lack of device-specific guidance documents and use of special controls for many devices. The agency could do a much better job of recognizing international and national consensus standards and of leveraging them in the review processes, Phillips said. And it is difficult to address safety and effectiveness issues related to legally marketed devices—a problem that is not peculiar to the 510(k) process but is also relevant to PMA products.

The agency has flexibility in that it can ask for whatever information its reviewers believe is necessary. The agency can also use the work of standards-development organizations in developing voluntary consensus standards. There is an opportunity, for a class I or II medical device to go to one of the dozen or so FDA-accredited third-party review organizations. Some may consider that having outside reviewers do FDA's work poses a vulnerability but, Phillips said, the work product comes to the agency for final review of a submission.

Premarket Notification vs Premarket Approval

Phillips stressed that the premarket notification, or 510(k), process is a classification process, whereas PMA is a determination of safety and effectiveness that leads to approval. Thus, the programs cannot be directly compared. For devices in class I and class II, safety and effectiveness are ensured by conforming with all the general controls. There must be verification that companies are in conformance with the controls and vigilance in

[3]Guidance is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080235.htm.

monitoring the performance of a device once it is in commercial distribution to determine whether it is performing as it was designed to. For the 510(k) process, devices are *cleared* for marketing, not approved, and devices may not be marketed as "approved by FDA."

PMA of class III devices involves device-by-device assessment. From concept to obsolescence, class III medical devices are subject to FDA conditions and requirements that their manufacturers are obliged to meet. These devices do receive approval by FDA.

Environmental Considerations

There is tremendous competition in the medical device industry, Phillips said. There is an emphasis on cost containment, and the practice of medicine places demands on the industry. Those environmental factors prompt the continual evolution of medical devices with regard to intended use and technology. That results in substantial regulatory challenges. An example is combination products, such as medical devices that are associated with a drug or biologic.

Closing Remarks

Phillips reiterated that ensuring the safety and effectiveness of medical devices is a complex task and that the 510(k) process is only one part of it. He urged the committee not to be misled by the concept of substantial equivalence; the issues are broader. The 510(k) process has strengths and weaknesses, but it makes important contributions to public health. Whether 510(k) is maintained as is, changed, or abandoned, the system of medical device regulation must be flexible enough to accommodate the constant and rapid change associated with the medical device industry and must have the integrity to withstand criticism. It is difficult enough for FDA staff to make decisions without having to operate in an environment in which people are second-guessing the underlying regulatory framework in which the decisions are being made.

Given adequate resources, Phillips said, changes could be made in how devices are classified, reviewed, and managed by FDA. The current framework in which the agency has to operate is sound. There are, however, major resource issues that create gaps, for example, in verifying compliance with general controls. Many manufacturing facilities of class I and class II devices are not inspected as frequently as they should be for good manufacturing practice. With regard specifically to 510(k), there needs to be additional emphasis on developing guidance for industry or special controls and a roadmap for bringing new and innovative products to market and removing the guesswork. The agency does not have the resources needed to look at the

500 or 600 class II medical devices each year and develop special controls for all of them or to develop guidance for all of them. Phillips stated that the system in its current form is fundamentally sound but that it could be improved in a number of ways to fill in the gaps and provide a higher level of assurance of safety and effectiveness.

THE FOOD AND DRUG ADMINISTRATION'S COMPLIANCE INFRASTRUCTURE

In the context of medical devices, compliance is simply conforming to the law, said Tim Ulatowski, director of the Office of Compliance at CDRH. FDA seeks a voluntary commitment to compliance by industry and others that must conform to the law but stands ready to enforce the law when it is necessary.

Some of the functions that fall under the heading of compliance are manufacturing-facility inspections, promotion and advertising, import control, bioresearch monitoring (for example, the evaluation of the conduct of clinical investigators, institutional review boards, and clinical sponsors), registration and listing (ensuring that all manufacturers are registered and that products are listed in the FDA system), recall monitoring and classification, premarket manufacturing review, enforcement actions, and education.

The hierarchy of decision-making related to compliance activities starts with the commissioner at the head of the agency, who is directed by the president and the secretary of health and human services. Within the commissioner's organization is the Office of Chief Counsel (reporting directly to the secretary), the Office of Regulatory Affairs (ORA), CDRH, and other centers.

ORA manages the regional and district offices and the field laboratories across the country. It is a well-staffed, well-organized office that consists of thousands of people who conduct facility inspections, among other tasks. Recall coordinators interact with companies as they conduct recalls of products. The field laboratories sample-test products for enforcement purposes. ORA manages import operations at the points of importation by interacting with US Customs and Border Protection, evaluating entries to determine whether they are legally able to enter the marketplace in the United States. ORA also coordinates overall FDA compliance and enforcement policy and has a criminal-investigations group that evaluates possible felonies and misdemeanor criminal cases.

Within CDRH, the Office of Compliance establishes the medical device and radiologic health compliance and enforcement policy and procedures. The office determines resource allocations in collaboration with ORA—for example, how to allocate inspection staff, how much will be spent on manufacturing inspections, how much time will be spent on mammography

inspections, how much time will be allocated for inspections that might need to occur on the spur of the moment because of a particular problem, and time spent on bioresearch monitoring inspections. The Office of Compliance classifies recalls, reviews communications issued by the manufacturers, and drafts and issues communications from the agency regarding recalls. It also develops strategies for inspections and inspection assignments, coordinates foreign assignments, reviews inspections and enforcement cases, and enforces promotion and advertising law.

The Office of Chief Counsel (OCC) evaluates the cases brought by ORA and CDRH for legal sufficiency. Cases then move to the Department of Justice, to be brought before a court. OCC also evaluates regulations, guidance, new initiatives, and advisory letters.

FDA can take a variety of advisory actions. At the time of inspection, a manufacturer may be advised of potential violations. If the violations are serious enough, warning letters are issued to notify companies or clinical investigators that they are subject to legal action if the violations recur. If another inspection identifies the same violations, FDA moves into the penalty phase of enforcement action.

Product-specific seizure is one enforcement mechanism. A product may be seized, and a seized product may not be moved until the violation of the product is removed or, most often, the product is destroyed or reconditioned. FDA may seek an injunction against a facility or company, which more often than not will be resolved through consent decrees rather than litigation. The company and FDA enter into a court-approved consent order for corrections, monitoring, and oversight of the company as it resolves the violations. Another option is civil money penalties. Finally, there are misdemeanor or felony prosecutions in cooperation with the FDA Office of Criminal Investigation.

Unlike PMA devices, 510(k) products are not subject to preclearance inspections. There is an exception to that, under 513(f)(5), for cases of "substantial likelihood that the failure to comply with such regulations will potentially present serious risk to human health."

Manufacturers that submit 510(k)s to FDA for clearance are subject to quality system inspections, bioresearch monitoring inspections, or medical device reporting–related inspections under FDA's surveillance inspection program. There are also for-cause inspections in cases of allegations, reports, or other signals that come to the agency's attention. Ulatowski noted that even if a company does not have to submit a 510(k) for a particular change in a device, it still must document changes, and those records are subject to review on inspection.

FDA compliance staff monitor information on the Web and review letters sent to FDA, most often by competitors who provide information about a product that is potentially being marketed without FDA clearance

or approval. The agency also looks for substantial new claims that are made without clearance. Investigational device inspections are conducted for clinical studies that may be submitted in a 510(k). FDA evaluates problems with imported products, including products subject to 510(k) clearance, and can detain products at the border, particularly if there is a violative inspection of a foreign facility. Most recalls are voluntary, whether of 510(k) or PMA devices, but on occasion FDA has exercised its mandatory recall authorities under the law. Additional 510(k)-related compliance activities in CDRH include sampling and testing of 510(k) products as needed.

Other components of CDRH monitor and evaluate the postmarket environment, not just from a manufacturing-environment standpoint but with reference to the clinical environment, trying to use information from all sources to gain an understanding of how products are performing in the marketplace. Ulatowski noted that FDA sometimes moves from surveillance to action, but the integration between these functions is not optimal.

FDA is trying to prevent problems, not only to react to them, and to identify issues related to risk as they emerge and deal with them strategically in a coordinated effort, not only with compliance activities but with educational efforts. Nevertheless, much time is spent in reacting to issues that come to light.

4

The Medical Device Industry Innovation Ecosystem

Part of the committee's charge is to consider how the medical device industry innovation ecosystem is helped or hindered by the 510(k) statute and regulation. Two speakers reviewed the current environment of medical device innovation, including the effect of the current regulatory framework on device development. Panelists then discussed issues related to the balancing of patient safety and innovation

STRUCTURE OF THE MEDICAL DEVICE INDUSTRY INNOVATION ECOSYSTEM

Pain, suffering, and death from disease still plague patients worldwide. Even where solutions exist, many are suboptimal, and there is much room for improvement. Fortunately, the US economic system has created incentives and resources to promote and reward innovation, said Josh Makower, consulting associate professor of medicine at Stanford University Medical School and founder and CEO of ExploraMed Development, a medical device incubator. That has created a medical device (also called medical technology) innovation ecosystem in which ideas can become realities that can affect health care.

Many innovations in technology and procedure come from practicing physicians who have firsthand experience with what works and what does not. Their inspirations can become products. Makower cited a 1988 Institute of Medicine (IOM) and National Academy of Engineering (NAE) report on new medical devices and noted that not much has changed in medical

device development over the last 20 years—many of the challenges identified by IOM/NAE in 1988 persist today (IOM/NAE, 1988).

How Innovations Are Brought to Patients

The medical device innovation ecosystem has multiple components:

- **"Fuelers"—**venture capitalists, investors, and public markets that support the process and invest in the innovators.
- **Innovation catalysts—**small startups, large companies, incubators, and other entrepreneurs that invent the technology or take a concept through to commercialization.
- **Regulators—**the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), third-party payers, and professional societies (which play a substantial role in patients' access to new technologies).
- **Consumers—**patients, physicians, and hospitals.

Innovation catalysts with ideas need resources if they are to advance their innovations to the product stage. Those resources come from the fuelers. Products then enter the regulatory system in the hope that they will leave it to be delivered to consumers (that is, patients, physicians, and hospitals). Marketed products produce revenue that is returned to the innovation catalyst and rewards the fuelers, consumers generate new ideas on the basis of experience with the products, and the cycle continues. All the players in the system are responding to their own sets of risks and rewards. As the risks and rewards change, the player's behavior changes.

The primary fuel for device innovation comes from venture capital. However, little of the total pool of available investment capital is invested in medical device innovation. When venture capital underperforms, or when the total public market is compressed, venture capital for device innovation is reduced. From 2008 to 2009, for example, venture investment in medical technology declined by nearly $1 billion. As the global economy struggles, companies that have valuable technologies for patients are struggling to find capital. Only when venture capital outperforms does more money flow in.

The survival of small companies is critical for delivering innovation to patients, Makower said. Most of the ideas that really change the practice of medicine come from small companies or individual inventors. Department of Commerce statistics show that in 2002, 3,725 of the 6,007 US medical device firms being regulated by FDA had fewer than 20 employees, and only 150 had more than 500 employees. Large companies commonly acquire small companies. That provides a larger company with the innovation that it needs to grow and provides a small company with capital and with access to

the large company's expertise in scaling up production and delivering patient solutions to a broader community. Public market success excites investors, who help to fuel the next round of innovation.

From a regulatory perspective, it is important to recognize that patients' access to new health technologies is affected not only by FDA marketing approval or clearance but by the reimbursement process, which is also difficult to navigate.

Ensuring Safety in New Technologies

Patient safety is delivered primarily through good quality systems, and the vast majority of problems in the field are related to quality. In a well-run company, quality systems are integrated into the design process and follow a product through its life cycle, from concept through manufacturing and into the field (Figure 4-1). What is key for patients and for advancing

FIGURE 4-1 Patient safety is delivered primarily through good quality systems. Design control designs quality into a product from the beginning of development. Quality systems follow the product through its life cycle into the market.

technology is a system that permits rapid iteration, because it is impossible to model perfectly all the ways that devices and technologies are used in the field. Companies need to be able to make improvements quickly on the basis of feedback from the field.

There are substantial differences between how drugs and devices are developed and how they are used in practice. Devices span from low-technology tools, such as tongue depressors, to complex devices, such as implantable defibrillators. One size does not fit all with regard to evidence requirements. Some devices that are cleared through the 510(k) process undergo clinical trials, but many do not require clinical trials to establish safety. In fact, many of the structures of clinical trials that are used for drugs would be unethical and inappropriate to apply to devices (for example, blinding or sham groups for a dramatic surgical therapy). And devices rarely have distant systemic effects.

The standard device product life cycle is 18–24 months; that is, a product is replaced by a new or improved product within 2 years. Such a fast life cycle occurs, however, only when the reimbursement and approval pathways have already been pioneered. It often is not until the third or fourth generation of a medical device that clinical significance and cost savings start to become apparent; this is because of the time needed for adoption of the technology.

The Costs of Bringing Devices to Market Today

Before any funding is expended on pursuing a 510(k) clearance or premarket approval (PMA), there is a basic burn rate, the amount of money that a company has to spend every month to continue to exist. In addition, for any given product, costs are associated with concept development, proof of concept (for example, bench testing and animal testing), clinical unit development, obtaining an investigational device exemption (IDE), safety and feasibility studies (for example, small-group human trials), pivotal trials, the 510(k) or PMA process, and securing reimbursement. Today, navigating a device through the 510(k) process from concept through reimbursement will cost an average of $73 million for overhead and development. The cost to deliver new technologies to patients via the PMA path has historically been 2 to 5 times as much as the cost for 510(k) products (especially more novel products), averaging $136 million.

As noted earlier, iteration is the key to improving patient outcomes. The use of predicates allows innovators to build on established clinical and scientific data and bring incremental innovations to market quickly. Generally, little new science comes into play for 510(k) products. However, incremental technology innovation does not equate to incremental clinical value. Transformational leaps are created through a series of small steps.

One 510(k) product that delivered important outcomes was the delivery of insulin via pump vs multiple daily injections.

Time is money, and delays along the pathway from concept to market can be financially too much for a company to bear. If it takes a year to get an IDE approved, rather than 1–3 months, that can add $10 million to the overall cost. If later in the pathway the product is reassigned to the PMA track, there may be another $28 million in costs. Added time and expense at any step can become severe in the aggregate.

The Current State of the Device Innovation Ecosystem

In the marketplace, physicians are the natural gatekeepers for new-product implementation. They are cautious adopters, interested in both clinical data and the potential for reimbursement for their services. Device innovation is patient-driven (not technology-driven), and only technologies that address important patient needs can succeed, Makower said.

If the regulatory process is too difficult, it will deter even the most talented and creative innovators from entering the system. Similarly, most venture capitalists and entrepreneurs will avoid investing in projects that will require a PMA (although these are often the ones that have the greatest potential to affect human health). Over the last 10 years the number, of original PMAs has been declining; overall, there has been a disturbing compression in innovation in this country, Makower said. Companies' expenses are increasing but not their returns. That reduces the financial returns to venture capitalists and decreases the likelihood that they are going to invest further in this sector. That, in turn, drives innovators out of device development. The net effect is that many valuable ideas and technologies never reach patients.

The medical device innovation ecosystem is fragile and extremely sensitive to changes in the cost of innovation, which is substantial, Makower concluded. The system is already under immense economic pressure. Innovation is driven by physicians and companies working together for the benefit of patients. The process is and must be iterative. The 510(k) process encourages multiple iterations, which can have a revolutionary effect on patient care. To ensure that safe and effective innovations sustain and improve patient health, regulatory systems must be predictable and reasonable.

Makower noted there has been much misunderstanding in the public press about the 510(k) process, some calling it a fast-track process and others believing that no 510(k)s involve clinical trials. Overall, the 510(k) system works well, and we should be looking at specific cases in which it did not work well—in which patients were harmed in some way—and ask what could have been done in those situations. The question is whether those are unique situations or require a global response.

Makower asked the committee to consider carefully whether the system needs to be fundamentally changed or whether it is only a question of opportunities for better management—for example, more resources, more and better-trained reviewers who have clinical expertise, a better process for resolving disputes fairly and promptly; synchronization of requirements between FDA and CMS that allows the reimbursement process to start earlier; greater investment in review of quality systems and less in premarket requirements for class I and II devices; and consideration of postmarket opportunities, such as unique device identification. Overall, Makower said, any recommendations should sustain innovation, improve predictability of the process, and not substantially increase cost or time to market.

EFFECT OF THE REGULATORY FRAMEWORK ON MEDICAL DEVICE DEVELOPMENT AND INNOVATION

David Feigal, vice president for regulatory affairs at Amgen and former director of FDA's Center for Devices and Radiological Health (CDRH), presented an overview of a commissioned paper that he prepared for the committee on the regulatory burdens required to bring innovative medical technologies to market.[1] FDA, Feigal said, is the nation's oldest consumer-protection agency. The public health goals of the agency include safe human experimentation, marketing of products that have demonstrated effectiveness relative to known risks, manufacturing quality, truthful claims, prompt response to hazards, and prompt response to unmet medical needs. The question at hand is how well those goals are met in the regulation of medical devices, specifically, class II devices.

The Overlapping Life Cycles of Scientific Innovation and Product Regulation

Drugs and devices are different in many ways, but there are enough similarities for the device regulatory pathway to have borrowed some of its framework from that of drugs. For example, the biocompatibility testing of devices is based heavily on toxicology testing of drugs. Drugs have interactions; devices have malfunctions. Patients may receive the wrong dose of a drug; there may be user error with a device. Most drugs are clinically studied, whereas most devices (which are in class II) are bench-studied. Drugs rely on good manufacturing practices, and devices on quality systems. Those parallels often tempt people to say that devices should be subject to more drug-like regulation, Feigal said.

FDA's most important regulatory tool, certainly on the drug and bio-

[1]The complete commissioned paper is available as Appendix D.

logic side, is market authorization. Consumer protections can be stratified as predominantly in the premarket part of the life cycle (safety experiments, premarket safety and effectiveness studies, and inspections focused on premarket research) as in the postmarket part of the life cycle (truthful promotion, adverse-event reporting, postmarket studies, and manufacturing inspection). When there are concerns, one's instinct often is to require more evidence before marketing (for example, larger clinical trials before approval).

Some scientific problems, such as emerging public health threats, have life cycles of their own. Severe acute respiratory syndrome (SARS), for example, emerged rapidly and unexpectedly in 2003. The life cycle of the science of an infectious public health emergency starts with an index case (which is usually missed). Evidence of community wide infection begins to appear, and scientists begin to collect specimens (blood, saliva, and urine) and to try to isolate the infecting organism. Initial diagnostics are developed, usually in public health laboratories as laboratory-based tests, and begin to be used in the epidemic. The public health response (for example, quarantines and case tracking), is aimed at effective control and avoidance of new cases. As happened with SARS, by 2006 there were no new cases, at least for this initial cycle.

Similar to the cycle of public health response to a new infection are a product development cycle and a regulatory cycle. Development of a diagnostic device begins with identification of the concept, which is followed by development of the diagnostic active ingredient (that is, the analyte specific for the infection). It is often necessary to work with nonclinical specimens. Then there is a period of clinical investigation, which is followed by manufacturing scaleup of the device, market approval, and widespread use. Not long after that, there will be a next-generation diagnostic device, and the cycle will continue. The discussion at the time of SARS was about how to develop a rapid diagnostic that could be used in airports as people get off airplanes to determine whether to quarantine them.

The public health response cycle and the product development cycle have to be well synchronized, and they are inextricably connected to the regulatory cycle. Diagnostics, among the most regulated devices, are not only overseen by FDA in the United States but regulated under the Clinical Laboratory Improvement Amendments.

Instead of thinking only about devices as premarket and postmarket, CDRH looks at device products as a core cycle of concept, prototype, preclinical or bench testing, clinical evaluation, manufacturing, marketing, consumer use, and obsolescence. Every part of the cycle informs another part. An noted earlier, these products are iterative, and it does not make sense to think of postmarket requirements for a product that may be off the market—replaced by the next-generation product—before postmarket

studies could start. It requires a different kind of thinking, Feigal said. The next generation's premarket studies are actually the postmarket studies for the current generation, and it is not yet clear how to manage this.

The science cycle that overlays the product development cycle is a multidisciplinary process that involves, for example, engineering, clinical science, statistics, quality systems, manufacturing, epidemiology, and postmarket surveillance (Figure 4-2a). The corresponding regulatory cycle incorporates, for example, requests for designation, device advice, early planning meetings, IDE discussions, pre-IDE meetings, determination guidance, the applications themselves, advisory committees, and medical device reporting (Figure 4-2b). When considering changing part of that cycle, Feigal noted, the committee needs to consider how the whole cycle may be affected.

Regulation of Class II Medical Devices

Risk Classification

Product risk classification can foster innovation if the regulatory requirements are proportional to risk, Feigal said. That is, if a less risky product has to go through less to get to the market, that creates a drive for innovation. The regulatory-review cycle length should be proportional to risk. The target cycle time for class II reviews is 90 days, compared with the PMA target cycle time of 180 days. Innovation is inhibited when the risk classification becomes uncertain, when it creates burdens that were not anticipated, or when the review cycle becomes long.

Feigal noted that FDA needs to clear 15 new 510(k) submissions on each business day to keep up with the 3,000–3,500 submissions that it receives per year; 5 or 6 years ago, he said, there were about 250 staff dedicated to reviewing 510(k) submissions. Simple mathematics shows that staff can spend no more than a few weeks in reviewing an application, assuming that they review full-time and do nothing else. (Staff effort for approval of a drug application, approval of a biologic license application, and the PMA process is measured in person-years, not person-days.)

Device Classification

Device classification depends on the device technology and the product claims. Guidance documents for many of the classifications help to make the process more rapid and predictable and to foster innovation. But over 1,000 medical device classification groups need guidance documents, and it is especially challenging to write guidance that will continue to be relevant to rapidly changing science.

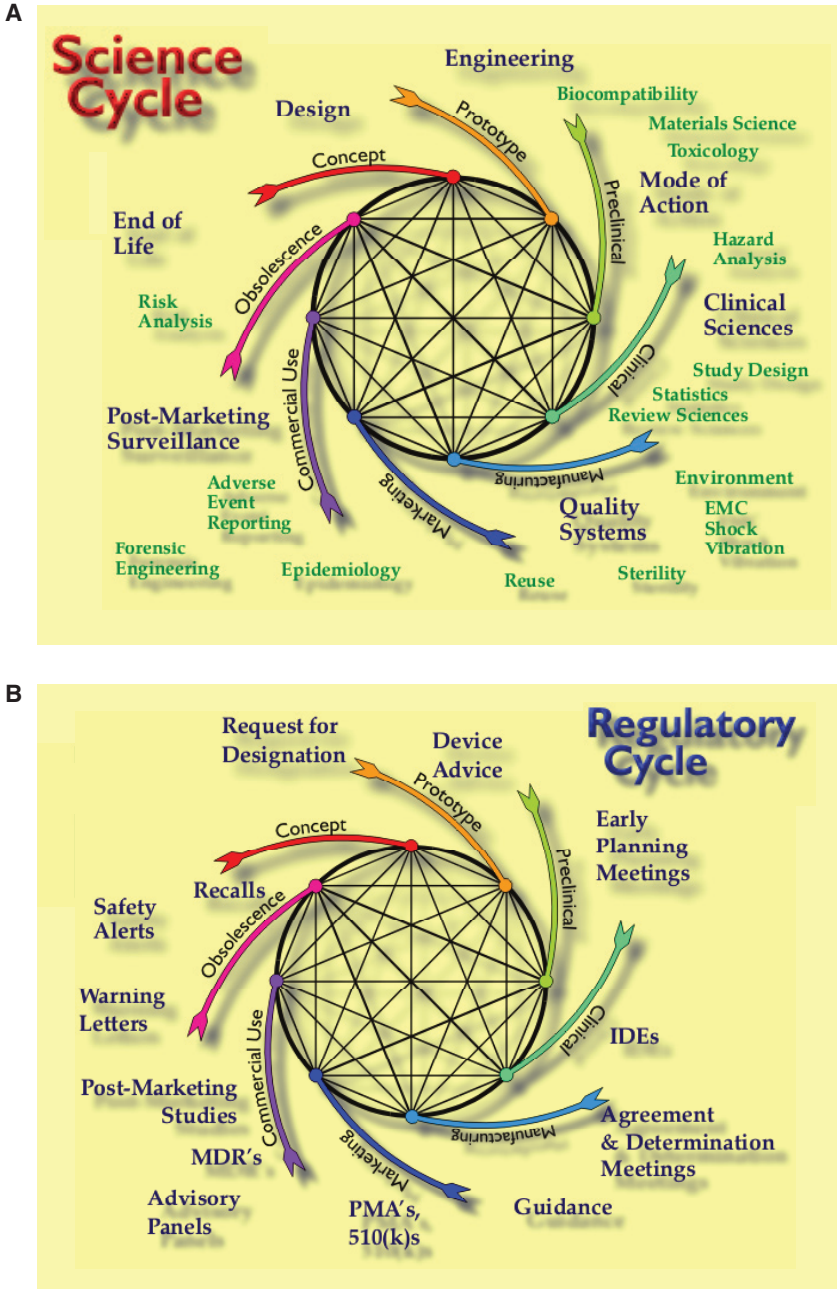

FIGURE 4-2 Total product life cycle—the science cycle (A) and the regulatory cycle (B).

Evidence Requirements

Evidence requirements are proportional to risk. The quantity and type of evidence required depend on the intended use of a product, and the 510(k) process of comparison with a previously approved product allows incremental improvements. A challenge for FDA is to manage functional or "tool" claims vs clinical claims. A functional claim requires less evidence, describing what a device does but not specifically which patient population it should be used for. There is concern that this approach creates a backdoor for technologies to be cleared without enough information about what they are going to be used for.

In addition to the evidence requirements, there are regulatory *standards* that help to simplify the review process. Evidence can be based on objective nonclinical performance criteria. In many cases, a performance assessment by an engineer or a physicist can provide more useful information about a device than a clinical trial. Although FDA makes a substantial investment in standards development, it is challenging to keep up. Standards are an important part of the assurance of the effectiveness of class II devices, Feigal said, and this function needs to be supported by adequate resources.

Clinical Evidence

Clinical evidence is needed more often for class II products than one might expect. Although a clinical trial may not be needed to establish safety and effectiveness, substantial equivalence sometimes can be evaluated only in the clinic. In other cases, there may be a need for clinical experience to address the human factors associated with the use and performance of a product; that is, clinical experience may be necessary to write effective training materials. Clinical evidence takes longer to obtain, and one approach could be to collect evidence across the entire class II product life cycle, not only before clearance.

Regulatory Incentives

For drugs and biologics, regulatory incentives, such as marketing exclusivity, encourage innovation. That approach is ill suited for the rapid changes and complexity of medical devices, Feigal said. Transparency is an important regulatory principle that promotes innovation and the adoption of safe and effective products. Transparency of the advisory-committees process and the transparency provided by guidance documents are strong development tools for innovators. One of the (somewhat controversial) proposals for increased transparency is that FDA make rejection letters public,

but there is some discomfort about the possibility that that would disclose trade secrets prematurely.

One of the principles of regulation is that claims are based on what is known. There is an incentive to know more, to have a better claim, and to secure a stronger market presence. The challenge is when to *require* that more be known as opposed to *providing incentives* to know more. That is, which information is important for the development of the medical knowledge base as opposed to essential to ensure safe and effective use? It is important to preserve the incentives and rewards that cultivate knowledge and to be cautions about requirements that might stifle innovation.

Biomaterials, Components, and Accessories

FDA struggles with the numbers and variety of biomaterials, components, and accessories in Class II products. There are often so many components in a device that it is impossible, for example, to remove components one at a time to see whether the product still works and what each component's unique contribution is. The final manufacturer is responsible for the whole device although components have many sources. FDA's challenge is to set priorities for oversight of manufacturers and their supply chains. It is important that standards not be so rigorous that we lock ourselves in to an existing technology and freeze out new technology in biomaterials and components, Feigal said.

Labeling

Class II devices are cleared on the basis of substantial equivalence to a predicate and so should have essentially the same labeling. That is counter to innovation. However, a class II device has to be "at least as good as . . .", so there is some ability to modify labeling to indicate the improvement over the predicate; for example, a new diagnostic device may be a "rapid" version of the predicate. In considering the 510(k) process, the labeling limitations for new class II devices should be taken into account.

Opportunities for Improvement

Feigal offered several suggestions for changes in the 510(k) process that would foster innovation in class II devices. First, he said, it is confusing to the public to have "cleared" products and "approved" products. FDA is approving class II products on the basis of a set of standards relevant to the class. There should be a separate class II approval process based on objective performance standards, clinical safety and effectiveness, and predicates that meet appropriate standards. Feigal recommended removing the reference to

pre-1976 devices from the statute. In handling class II products, he said, there are times when it would be better to rely on absolute performance standards rather than a predicate. Feigal also supported harmonizing the US quality-system regulations with the International Organization for Standardization Standard 13485 requirements and allowing mutual recognition.

Feigal suggested a variety of opportunities for FDA to foster innovation. The agency can work toward streamlining the risk-classification process to keep up with science. There is a need for guidance on all product classifications. It is also important to use evidence from the whole life cycle in decision-making. Regulatory decisions need to be science-based, not legislation-based. The law sets the framework, and the decisions are based on science. Peer-review regulatory decisions could enhance consistency and quality. These opportunities could be incorporated into the agency's review practices. Some lags in transparency, particularly in connection with Freedom of Information requests, can be fixed.

A part of the life-cycle map that is inadequate for 510(k) products is the postmarket period. More information is collected on PMA products than 510(k) products once they are on the market. Postmarket information is collected for PMA products, for example, in annual reports, periodic safety reports, and tracking reports. Some version of those could be used for 510(k) products. In addition, when a company decides to make a change in a product that does not require a new 510(k), it could submit general information about the change to FDA. It would not submit the whole set of changes that it documents internally but would keep FDA informed that the product has changed—for example, in a surface coating. If FDA sees a change in postmarket event reporting, it will know if there was a change in the product. Currently, FDA can learn about such minor changes on inspection, but it does not have enough resources for inspection. That would be one way to achieve better information flow. In addition, FDA does not know which products are in use and which ones have been withdrawn. Collecting information in this part of the life cycle is challenging. Notification of some events, such as withdrawal from the market, should be required.

In summary, Feigal said, risk-based regulation tailored to the specific nature of different class II devices is an appropriate way to protect the health of the public while encouraging innovation. Changes in the 510(k) process should strive to foster innovation, ensure confidence that the process has integrity, and bring to market tools and technologies that offer benefit with well-understood risks.

Panel Discussion: Balancing Patient Safety and Innovation

After the presentations, Makower and Feigal were joined by Hutt, Ulatowski, Phillips, and three other panelists: Amy Allina, program and policy director of the National Women's Health Network (NWHN); Bruce Burlington, an independent consultant, former executive vice president for regulatory affairs and human safety and quality at Wyeth, and former director of CDRH; and William Vaughan, a consultant to Consumer's Union on FDA issues, formerly staff of the House of Representatives Committee on Ways and Means, and staff director for the minority on the House Subcommittee on Health.

There was much discussion of the evidence base for device decisions. Panelists discussed how much evidence is enough for using products that are cleared through the 510(k) process and how such evidence should be obtained. Panelists also discussed how in vitro diagnostics fit into the medical devices structure, the need for consistent decision-making in classifying devices, and FDA's role as an enforcement agency.

Evidence Base

Allina described the mission of the NWHN as working to bring the concerns and needs of women consumers to the health-policy and regulatory discussion. In addition to safety and effectiveness, consumer advocates are concerned with innovation, seeking development of better products and sometimes of products that are already approved outside the United States. One question raised during a presentation was, How high should the regulatory bar for evidence be set without risking the blocking of patient access to innovative products? A parallel question, Allina said, is, What are the effects in patient harm and dollars wasted on ineffective products if the bar is set too low?

What does it mean for a product to be effective? Allina offered the example of home uterine-activity monitors, which some pregnant women are instructed to use if they are at risk for preterm birth. The manufacturer did not have to show that using a home uterine-activity monitor would make a difference in preventing preterm birth, but only that it worked as it was intended to work. Ultimately, a study by the National Institute of Child Health and Human Development found that the monitors are not useful in predicting or preventing preterm birth, the American College of Obstetrics and Gynecology concluded that they should not be part of standard care, and the Agency for Healthcare Research and Quality advised against using the products because they confer no maternal, fetal, or neonatal benefits. FDA needs the authority, Allina said, to require companies to provide relevant efficacy data. Otherwise, health-care dollars are being wasted, and

patient harm can result. The FDA needs to know that it can use its flexibility to meet patient safety demands, not only to respond to the concerns of commercial sponsors, she said.

Makower responded that physicians should be using clinical data to drive their decision making and that FDA should not be preventing them access to a device if they decide that it is good for their patients. The question, he said, is, Where is the line between when there are enough data to allow a product onto the market and when the responsibility of the physician begins? Information is the key. If FDA said that "this is commercially available, but there is no evidence to support X, Y, and Z," that would have a powerful effect on a product's utility.

Hutt added that the laws do allow FDA to require clinical utility; that is part of "substantial equivalence." With home uterine monitoring, he said, there was a requirement for a clinical trial, but the end point that was chosen was whether the device allows a doctor to obtain information earlier and therefore be able to intervene to prevent preterm birth. It may well have been the wrong end point to choose, but there was no lack of statutory authority or of clinical trials in this case.

In review of 510(k)s, Ulatowski said, much time is spent in trying to figure out what questions need to be answered; for example, Is it materials or clinical utility? What is necessary in the end point?

Hutt referred to the Cooper Committee report, which strongly concluded that the type, quality, and quantity of evidence required for devices were different from those required for drugs. As a result, the 1976 device statute contains different language regarding the safety and effectiveness of devices from the 1962 statute addressing the requirements for drugs.

Economics come into play in evidence requirements. Hutt asked whether a device company could afford a $50 million or $100 million controlled clinical trial for a medical device that does not have nearly the market value of a blockbuster new drug. High economic barriers harm innovation. The corollary question, Burlington said, is whether we can afford to have products on the market on which there is not enough information about proper use or even on whether use of the device provides more benefit than risk. Allina added that although NWHN advocates for new alternatives to existing products, no one is helped by approving or clearing more products on which there is not enough information about use. The challenge for FDA is to identify the middle ground.

A committee member asked whether Hutt, if he were to rewrite the 1976 amendments today, would consider requiring more scientific evidence regarding the safety of medical devices. Hutt responded that structurally, he does not see a need to change anything in the current statute. FDA can require whatever data are needed to show safety and effectiveness. The amount of data required is, and should be, a matter for FDA discretion.

Trying to legislate the level of evidence required would inevitably set the bar at the wrong place. It cannot be accomplished by statute, regulations, or guidance but only by individual reviewers case by case. Allina said that it is important to empower the agency to make those decisions on the basis of science and noted that FDA could use more direction in setting that bar.

In considering changes that could be made in the 510(k) process, Feigal encouraged the committee to look for ways to create incentives and rewards for accruing information as a product evolves and the science evolves over the course of the product life cycle. For example, digital mammography was first allowed onto the market for use in patients that were referred because of an abnormality. It was not clear at that time whether the technology would also be good for screening. Four companies agreed to conduct a 40,000-patient study funded through a public partnership with the National Institutes of Health. FDA created an incentive for the study by saying that unless one of the devices was a particular outlier, it would make a single decision for the group of products. The companies would not be allowed to compare each other's products on the basis of data from the trial; the clinical utility of digital mammography for screening would be established as a group. When the study was completed, the data revealed findings that would not have been apparent in a small study, for example, that there were advantages for some groups of women with respect to detection. Those types of studies cannot be done every time, but the example shows that some questions can be answered only with large, multisponsor trials.

Burlington asked whether, as a result of the current financial situation, FDA is being forced into a system in which, to get companies to innovate, it needs to allow products to enter the market quickly and easily. Are products being developed in the marketplace rather than before they are put onto the market? Makower said that device companies are constantly solving problems and in the process learning new science and discovering new problems to solve. Feigal noted that the first blood-screening test for hepatitis C had only had about 60 percent sensitivity. The blood advisory committee recommended not telling blood donors their test results but using the test only to screen donor blood and destroying any blood that was probably infected. That was before treatments were available. Eventually, knowledge about hepatitis C infection accumulated, and treatments were developed. But it had been right to try to prevent transmission of hepatitis C through blood products even though the tools were less than ideal. That is the iterative nature of the development of medical products.

In Vitro Diagnostic Devices

Does it make sense, Burlington asked, to use the same regulatory framework for both diagnostic and therapeutic devices? If so, why is it appropri-

ate for FDA not to regulate the central laboratory–based high–information-content diagnostics?

Feigal said that inaccurate information from in vitro diagnostic tests can be as dangerous as a faulty medical device. If a diagnostic product yields an erroneous cancer diagnosis and the diagnosis is acted on, it is the information that has caused harm. One of FDA's problems occurs when regulatory systems overlap. In this case, there is a gap between supervision of laboratory processes under the Clinical Laboratory Improvement Amendments and FDA supervision of in vitro diagnostics.

Phillips said that the FDA Office of In Vitro Diagnostics regulates diagnostic tests a bit differently from other products because the concept of substantial equivalence has evolved differently in relation to the two. There is less emphasis on substantial equivalence and more emphasis on characterizing the performance of products (for example, sensitivity, specificity, and accuracy), and there is a standardized regimen for assessing how products perform. In addition, a specific labeling regulation that governs in vitro diagnostics does not apply to other products.

Diagnostics are somewhat different, Feigal agreed, but the fundamental problem of having enough information is the same.

Consistent Criteria for Assigning Device Class

One particular issue of concern to NWHN is the lack of consistent criteria for determining what goes through the 510(k) process. Companies that were developing female condoms, for example, initially sought to use the 510(k) process, with the male condom as a predicate device. Of course, there are some obvious differences, and a female condom raises questions that would not have been asked in approving a male condom, Allina said. NWHN argued, and FDA agreed, that female condoms should have to go through PMA. But there was a great deal of confusion, controversy, and delay. The lack of clarity was a problem for the company, for FDA staff, and for women. As a result, FDA convened a group of product developers, consumers, and scientific experts to help them to develop guidelines for contraceptive-device approval. The new guidelines were helpful but did not solve the problem of inconsistent decision-making across the board. Later, when a female-condom manufacturer wanted to return to FDA with what appeared to be a simple materials change, it was required to go through PMA. In light of the existing vagueness and flexibility, as things change environmentally there is no consistency within the agency.

No one would disagree that greater consistency is needed in everything that FDA does, Hutt said. But he noted that achieving that goal is extremely difficult in what is now an over 12,000-person government agency that makes numerous decisions daily.

Enforcement

Burlington raised the question of whether the current enforcement regimen is an efficient or effective way to ensure to compliance. The agency has the authority to issue civil financial penalties, but the process is cumbersome and inefficient. Ulatowski responded that FDA has lost the efficiency to take actions quickly (for example, product seizures), and he supported the commissioner's current efforts to revitalize the enforcement program. The tools for enforcement exist, but there could be greater efficiency in using them. It would also involve training staff to be more effective. Hutt added that although FDA is built on science, it is not a science agency. Its true mission is law enforcement, and the failure to bring strong enforcement action is a signal that the agency does not stand behind all its requirements to the degree that it should.

Additional authorities and resources are much needed for antifraud efforts, Vaughan said. Those resources will probably come from user fees, and this presents a conflict because an industry that funds an agency can have influence on the agency. User fees should not be associated with specific agency performance requirements, he said.

Participants discussed the extended length of time between inspections of foreign plants that manufacture class II devices and the need for more resources to tighten oversight. Burlington noted that public firms have to disclose financial information quarterly and annually and must have their disclosures attested to by an independent accounting firm. Perhaps a similar system for device compliance might be effective: disclosure by the company reinforced by an independent third-party audit and backed up by FDA, which would oversee the auditors and introduce sanctions when they are needed. That is essentially the system that is used in countries that require International Organization for Standardization Standard 13485 certification, Feigal said. Companies provide compliance information to the government before they file some kinds of applications, or they have independent audits of their quality systems. Such an audit is one way to keep up to date and avoid the problem of the 5- to 7-year inspection cycle. Feigal noted, however, that he sensed a strong preference in FDA for conducting inspections itself rather than through third parties and self-certification, in part because FDA, as a law-enforcement agency, has the responsibility.

REFERENCE

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5

The Global Framework for Regulation of Medical Devices

The final session of the workshop focused on how other countries have dealt with some of the medical device regulatory issues that were identified in the United States. Speakers and panelists discussed the global regulatory environment and past and current efforts toward global harmonization.

Comparative Overview of Medical Device Regulatory Systems

David Jefferys, a medical device expert and senior vice president for global regulatory, health-care policy, and corporate affairs at Eisai Europe, Ltd., provided an overview of European device regulations and discussed some of the key procedures in Japan, China, and India and how they differ from current operations in the United States.

European Regulations

In Europe, four directives cover the medical device sector. A directive is an instruction to the member states of the European Union (EU) to implement a law through national regulations. The first directive, 90/35, was concerned with active or powered implants. It was followed by the main general medical device directive, Directive 93/42, and then more recently by Directive 98/79, which covers in vitro diagnostics, and Directive 2000/70, which covers human blood and plasma derivatives. The date of a directive is not the implementation date, Jefferys noted. The general medical device directive of 1993, for example, was not fully implemented until the end of 1998, and the in vitro diagnostic directive of 1998 did not become fully

operational until 2001. More recently, in an effort to consolidate the texts, Directive 2000/747 was issued to bring together the four others and was an "updating directive." More detailed implementing directives (there are five in Europe) will be enacted by the European Commission, taking into account the views of the member states. There is also Advanced Therapies Regulation 1394/2007, which is automatically binding on the member states and does not have to be transposed into national law.

Those directives are known in Europe as New Approach legislation. That legislation covers all consumer goods except pharmaceuticals. (Legislation concerning pharmaceuticals has been in place since 1965 at the European level since the thalidomide disaster.) The New Approach incorporates self-regulation and imposes the minimum level of regulation that is necessary to protect public health. The legislation reflects the dynamics of the device industry, which are different from those of the pharmaceutical industry.

Key features of the device regulation are that the legislation sets out what are known as the essential requirements, the core elements and procedures that companies need to have in place; sets out and defines the conformity assessment process (how independent bodies will assess whether a device is in conformity with the directives); and lays down precise obligations on the part of manufacturers. The legislation establishes "notified bodies" to evaluate devices and "competent authorities," which are the agencies that control clinical trials, designate and supervise the notified bodies, and oversee postmonitoring surveillance. The legislation itself is underpinned by "normative standards." Some are European standards, others are International Organization for Standardization (ISO) standards, and some are parts of a series of European guidelines called MEDDEV.

The European system is similar to the US system in that it is a risk-based device classification system, Jefferys said. In Europe, there are three classes but four categories:

- **Class I—**self-regulation (and registration in each member state where they are marketed).
- **Class IIA—**selective quality-system review (QSR) (for example, measuring devices and sterile products).
- **Class IIB—**full QSR and targeted review of the design dossier (devices are defined in legislation and are not open to interpretation).
- **Class III—**full design-dossier review.

Competent Authorities

Each member state in the EU has a competent authority; these are the same agencies that regulate pharmaceuticals (except in the Netherlands).

The first role of the competent authority is to designate and then to supervise the notified bodies (and on occasion to withdraw the approval of a notified body or restrict it). A notified body falls under the supervision of the member state in which its headquarters is; however, at the EU level, the Notified Body Operations Group (NBOG) sets the criteria for inspection and coordinates training and supervision for the shared audits of the notified bodies.

Clinical trials for devices in Europe are controlled by member states under a competent authority. Another role of a competent authority is compliance and enforcement, ensuring that the Medical Devices Act is being complied with and potentially prosecuting anyone who places a device on the market without authorization or a device that is inappropriately labeled. A competent authority also supervises class I devices. Although there is self-regulation, there is a program whereby the agency will visit a manufacturer and review its dossier to make sure that the company's self-regulation is appropriate. Some of the audits will be unannounced, others will be targeted around complaints or result from vigilance reports or adverse incidents.

Notified Bodies

The notified bodies have a variety of backgrounds and competences. As defined by the directive, notified bodies may cover all consumer products or may be selective. As described above, they are supervised by the competent authority of a member state and by the NBOG. Each has a detailed published policy of conflicts of interest regarding internal staff and expert panelists.

In Europe, a manufacturer chooses one notified body, which then undertakes the evaluation of the manufacturer's product. Evaluation is done once for all Europe. The manufacturer pays the notified body for this service. For example, a German company can go to a Spanish notified body; once the notified body is satisfied, it allows the company to apply the European Conformity (CE) mark, the product is placed on the register (with a note indicating the number of the notified body), and then the product can circulate, with appropriate labeling, anywhere in the EU, the European Economic Area, and some other countries that have mutual agreements with the EU, such as Switzerland and Turkey. Jefferys noted that with good systems of quality assurance there is no concern about a conflict of interest associated with a manufacturer's paying the notified body for review of its product. The notified body is inspected and supervised by a government agency, so there is a separation, with respect to quality assurance, between those doing the evaluation and those evaluating the evaluation.

Most companies build a relationship with one notified body, and that notified body will inspect its quality systems, risk-management systems, and

other aspects of its operation, Jefferys said. The notified body lives with the product and with any variations or change in the product, and it is involved if there are any vigilance problems.

Many of the notified bodies play an international role, are qualified under the Conformity Assessment Body system to bring a product into the United States, and have a role in the systems in China and Japan.

A notified body assesses only whether the device works according to the manufacturer's claims. Other bodies will determine whether the device represents a good use of public money and how it fits with other devices, therapies, or interventions already used in the health system.

Postmarket Surveillance in Europe

There are two systems for postmarket surveillance in Europe: the mandatory vigilance procedure and the user reporting system. The vigilance procedure follows the Global Harmonization Task Force (GHTF) Study Group 2 guidance and is compulsory for manufacturers. Evidence suggests that manufacturers in Europe probably report twice as many cases as they need to. Electronic reporting is now used in many member states. The competent authority of the member state in which an adverse event first occurs will become the lead to coordinate European action. The legislation includes a safeguard clause whereby a member state that is particularly concerned can suspend the CE mark with immediate effect, but that action then must be referred to the European Commission within 15 days for a European view.

The user reporting system is built largely around the fact that health care in almost all member states is paid for and generally run by the countries concerned. It is therefore expected that health-care professionals will report adverse events to the competent authorities. Patients are also encouraged to report adverse events directly. In some member states, there is now a system of liaison officers, designated staff members in the health system who are responsible for seeing that health-care device alerts are received and implemented by all health-care professionals. Liaisons are also responsible for quarantine procedures in the event of a device recall.

In many member states, registries allow all patients with a particular device to be followed—for example, joint implants, cardiac pacemakers, heart valves, coronary stents, breast implants, and cephalic shunts. Many member states also have national electronic record databases, which allow consolidated collection of information over a patient's life span.

Jefferys noted that the European system allows a device's classification to be upregulated and downregulated as experience accumulates.

Specific Device Issues

In Vitro Diagnostics

The in vitro diagnostics directive has two annexes: annex 1 requires manufacturers to supply the information necessary for the safe and proper use of the device, and annex 2 is a defined list that includes, for example, blood reagents, anything to do with HIV testing, hepatitis testing, and any over-the-counter device that is for self-monitoring, such as blood-glucose monitoring. But many tests that are left out of annex 2 should perhaps be included, Jefferys said, such as biomarkers and genetic tests. There is a move in Europe to make in vitro diagnostics subject to a more risk-based classification system.

In Europe, as in the United States, there are issues related to "home-brew" test kits and to the balancing of compliance with the needs of innovators and health-care professionals, who develop or adapt diagnostic devices as situations require.

Combination Products

Combination products are the subjects of active regulation, Jefferys said. Recent research suggests that up to 30 percent of pharmaceutical research and development is now directed toward combination products. There are three basic groups of these products: drug–device combinations, which fall under pharmaceutical law; device–drug combinations, where the lead is device law; and diagnostic–drug combinations or "companion diagnostics," which Jefferys said may require new legislation to be appropriately handled.

For a device that administers a medicinal product, in Europe as in the United States, the concept of "primary intended purpose" is used. Simply, the medical device directive applies if the device components to deliver the drug could be used separately, such as syringes and infusion pens. A notified body is obliged to get an opinion from a pharmaceutical competent authority. However, if the device and the medicinal product form an integrated element, the product will be covered under the pharmaceutical law, for example, prefilled injectors, such as the EpiPen, in which it is clear that the device is to be used only once for delivering the pharmaceutical product contained.

Some combination products are medical devices that incorporate a pharmaceutical substance with an ancillary action, for example, drug-eluting stents. Those are handled under the device law, but the opinion comes from the drug authority, who looks at the safety, quality, and usefulness of the product. Usefulness, which is determined by a notified body, is

the basic rationale for the product, in light of the contribution that is made by the product, but not the efficacy or the performance itself.

In Europe, Directive 2000/70 deals with combinations of device with stable blood products. That would seem to be a small category and one that might not merit a separate directive, but it was meant to be the legislation that would capture tissue engineering. However, there was not political agreement, and all that was left was a piece of legislation on stable blood products. A combination that involves a blood product is subject to a mandatory consultation with the European Medicines Agency (EMA), not the individual member states.

In summary, there is no European counterpart to the US Food and Drug Administration (FDA) Office of Combination Products. Instead, it is necessary to involve both parts of the system—notified bodies and competent authorities—as appropriate.

Advanced Therapy Products

Europe has legislation regarding advanced therapy products (regulation 1394/2007EC), which covers tissue engineering, cell therapy, and gene-therapy products. The latter two, Jefferys noted, were already controlled under pharmaceutical legislation but have now been brought together with tissue engineering, or human viable cell products, to be included in the regulation of advanced therapies. The legislation covers both allogeneic and autologous products. The Committee for Advanced Therapies has been established and reports to the Committee on Human Medicinal Products in the European Medicines Agency.

Borderline Products

As in the United States, regulations cover medical devices, pharmaceuticals, advanced therapy products, cosmetics, biocides, personal protective equipment, and foods and nutraceuticals. Among each of those, there will be products on the border between classifications (for example, artificial saliva and medicinal wipes). A guideline gives examples of borderline products that are classified as medicines or devices. A product cannot be covered under more than one piece of legislation, so a decision must be made to regulate it under the pharmaceutical or the devices directive.

Japan

Japan has been changing both its pharmaceutical and its device legislation, Jefferys said, working toward following the GHTF classification (additional details about the GHTF system are presented later in this

chapter). How the Pharmaceutical Affairs Law classifies medical device products generally overlaps with the GHTF system. But the Japanese, like the Europeans, have been using third-party certification for class II devices, and Japan has designated 12 certification bodies. Japan's Ministry of Health, Labour and Welfare (MHLW) receives a dossier at a superficial level and decides whether it is appropriate for third-party assessment. After reviewing a favorable report from a third-party assessor, MHLW issues a certificate. Using the GHTF principles, the third-party assessors use the Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) for the product application. By the end of 2011, all class II devices will be handled by third-party certification.

Overall, Japan is moving forward in a fashion similar to that in Europe, Jefferys said.

India

In India, medical devices are regulated under the pharmaceutical law by the director general for pharmaceuticals. After extensive consultation, India is introducing comprehensive medical device regulation. Modeled largely on the GHTF, it has the same four classification categories, from low risk to high risk, and will involve a conformity-assessment process, self-regulation, notified bodies, and quality system review, similar to those in Europe. The only difference, Jefferys said, is that India uses type testing, in which is a designated laboratory tests devices. The new legislation is expected to be in place within the next 12 months.

China

In China, medical devices are controlled by both the central State Food and Drug Administration (SFDA) and local provincial controls. The system is risk-based and similar to that in India in that class II and class III devices undergo sample testing (type testing) in an approved laboratory. Selected products are required to undergo further clinical evaluation in designated SFDA-approved hospitals.

The SFDA has its own evaluation center and its own expert technical committees. Chinese regulations require a local, Chinese-based distributor. Inspections are handled by provincial authorities. In the case of overseas manufacture, the country of origin must attest its approval. For example, a US-based company cannot bring a new device into China if it is not already registered with the US FDA.

PAST, PRESENT, AND FUTURE GLOBAL HARMONIZATION

Janet Trunzo, the executive vice president for technology and regulatory affairs at AdvaMed and a member of the GHTF steering committee, provided an overview of efforts to harmonize regulatory approaches for medical devices. The call for harmonization came from various stakeholders, including governments, industry, and the public. Harmonization provides for consistent application of regulatory principles and approaches and improves regulatory-system effectiveness and efficiency. There is a reduction in duplication of regulatory activities, which can lead to time and cost savings. New products and technologies enter the marketplace in more streamlined fashion, and there is more transparency in the process.

Many regulatory programs use international standards and guidelines as a basis of their national technical regulations. Trunzo noted that many FDA staff have participated on some of the regulatory-standards committees. It is also important that regulatory systems seek input from stakeholders in the process of harmonization.

The GHTF is a voluntary group that was established in 1992 as a partnership of the regulators and the regulated industry. The founding members were the United States, the EU, Canada, Australia, and Japan. There are liaisons with other bodies throughout the world, including the Asian Harmonization Working Party (AHWP); GHTF has memoranda of understanding with the ISO and the International Electrotechnical Commission, and it works directly with the World Health Organization and the Pan American Health Organization.

The purposes of the GHTF were to encourage convergence in global regulatory practices and to promote technologic innovation and international trade through harmonized regulatory processes. The task force was also designed to serve as an information-exchange forum. (The GHTF does not evaluate the effectiveness of regulatory systems worldwide.)

Structure

The GHTF is governed by a steering committee composed of four regulatory representatives and four industry representatives of each of three geographic areas—North America, Europe, and the Asia Pacific (total, 24 members). Leadership of the steering committee rotates every 3 years. In addition to the steering committee, which directs the work of and defines the strategic plan for the organization, there are five study groups and ad hoc working groups as needed.

Study group 1, the premarket study group, developed many of the documents that were the basis of the harmonized regulatory model. Study group 2, which focused on postmarket issues, had a role in developing the vigilance procedures and adverse-event reporting. Quality systems, the focus

of study group 3, are based on the international standard for quality-management systems, ISO 13485. Basic auditing processes and the standard audit-report format were developed by study group 4. Study group 5 focused on clinical evidence.

A primary subject of activity is principles of classification, especially the establishment of a common vocabulary. Other basic subjects include technical requirements, format and content of marketing applications, assessment and review practices, postmarket activities, and quality-management system requirements and auditing functions.

Ad hoc working groups have been established on medical device software, combination products, training, the global regulatory model, global medical device nomenclature, unique device identifiers, and improvement of GHTF administrative processes.

Accomplishments

Trunzo highlighted several key accomplishments of the GHTF. First is the development of a harmonized regulatory model. Countries that are developing device regulatory systems can use the model as a reference. The model incorporates principles of risk-based classification, harmonized definitions and vocabulary, global medical device nomenclature, the STED format for marketing applications, assessment and review practices, quality-management system requirements, postmarket activities, use of international standards, adverse-event reporting requirements, and the National Competent Authority Report (NCAR) exchange program.

The document on principles of classification contains basic principles, but they can be modified by looking at the history of a particular product and considering whether it can be moved into a lower class or a higher class. (It is not based on any kind of predicate system, Trunzo noted.) The principles were defined to allow approval of a product through regulatory systems (for example, notified bodies for the moderate-risk classes); they include basic principles, essential requirements, and conformity-assessment principles for facilitating a determination of whether a product should go onto the market. In its documentation, Trunzo said, the system complements what occurs in the US regulatory system.

With regard to postmarket activities, the GHTF has provided basic guidance in collecting adverse-event reports, the report format, taking field corrective actions (for example, recalls), and vigilance reporting. Part of postmarket activities is the NCAR program whereby regulatory agencies exchange reports of adverse events in their countries. To participate, a country must have an adverse-event reporting system, must be trained by the members of the GHTF who administer the program, and need to understand the various levels of regulatory action.

The GHTF has created over 30 guidance documents that describe all the regulatory processes noted above. There is a consultation system on the GHTF Web site for any guidance document that is proposed and comments are accepted from stakeholders. Every comment is formally addressed by the study group that developed the document. The GHTF is also asked to provide regulatory training on the basic elements of its regulatory model. Trainers are mostly volunteers who work for regulators and the industry.

Challenges

A question often heard at GHTF conferences is why FDA has not fully adopted the GHTF model. The answer, Trunzo said, is that FDA had a regulatory system that was far more mature than any of the regulatory systems of other GHTF founding members. But there is a commitment from the members of the GHTF steering committee toward convergence of their regulatory systems as much as possible with the principles of the GHTF regulatory model.

Another challenge is related to conformity assessment vs type testing. Some countries still want to do type testing, but this is contrary to the quality-management-systems approach. In a quality-management-systems approach, there are procedures that build quality into the system, the product, and the design controls. One cannot test for quality one test at a time, Trunzo said.

In the United States, quality-system regulation is based on the ISO 13485 system adopted by the GHTF, but the QSR is still slightly different. Convergence in this field would be a good step forward, Trunzo said.

Determining when submission of clinical evidence is necessary and the elements that make up clinical evidence is another challenge. The GHTF study group 5 guidance document tries to provide some framework to address this issue.

Finally, adoption of global nomenclature is essential for progress, and continuing funding is needed for GHTF training.

The Importance of the Global Harmonization Task Force's Work

The guidelines that have been created by the GHTF provide a scientifically sound and internationally harmonized means of establishing quality, safety, and efficacy. The results are improved transparency, predictability, and efficiency of the medical device review process. Harmonization reduces regulatory burden and promotes industry compliance.

The work done by the GHTF promotes trade, innovation, and a more modern risk-based approach to regulation. Harmonization also creates a level playing field for industry in all countries. The GHTF promotes

regulatory communication and cooperation, providing opportunities for regulators to understand what is going on in other countries and for those developing regulatory systems to learn from others' experiences. Harmonization facilitates earlier availability of new technology and helps to avoid differences in technical requirements. The GHTF fosters productive working relationships among regulators, industry, and other organizations.

Adoption and Expansion of the Global Harmonization Task Force Model

The GHTF founding members are committed to moving their regulatory systems to the GHTF model. The AHWP, which has representatives of 20 countries, has developed its regulatory systems on the basis of the GHTF model, and the Association of Southeast Asian Nations (ASEAN), a group of 10 nations, has agreed to adopt the GHTF model. The Latin American Harmonization Working Party also participates actively in the GHTF.

Expansion is an important factor for the GHTF, and it involves more training and more wider adoption of the guidance documents that have been developed by the GHTF to facilitate broader implementation of the GHTF model. There are also efforts to translate GHTF guidance documents into other languages.

The GHTF has accomplished much in the last 18 years, Trunzo concluded. GHTF discussions today lead to a common regulatory framework of the future. Building on that foundation, we can move forward to the realization of global harmonization.

THE PRICEWATERHOUSECOOPERS MEDICAL INNOVATION TECHNOLOGY SCORECARD

Trunzo presented an update on the development of a "medical innovation technology scorecard" by PricewaterhouseCoopers (PwC) on behalf of Doug Mowen, managing director of medical device industry practice at PwC, who was unexpectedly unable to attend the workshop.

The goal of developing the scorecard is to inform all medical device industry stakeholders about why the innovation model for medical devices is unique. The project, sponsored by PwC, was announced in spring 2009 at an international conference in Rome, and it is expected to be completed in fall 2010. The final product will be presented at the AdvaMed Technology Conference in October 2010 in Washington, DC.

The framework of the scorecard consists of two basic elements, Trunzo explained. The first is information on the regulatory environment (including policy, compliance, payment, and reimbursement), which is being collected through a survey of medical-technology companies. The second element is a collection of information from publicly available sources (such as the World

Bank) regarding access, demographics, and market factors (Figure 5-1). The markets being studied are the Brazil, China, France, Germany, India, Israel, Japan, the United Kingdom, and United States. All those countries, Trunzo noted, have much medical device technology development.

The questions in the survey are generally focused on infrastructure and investment in medical technology. One question that is being asked with regard to the regulatory environment, for example, is which regulatory and reimbursement environments are the most attractive for the introduction of innovative medical technologies. On access, the survey asks which countries are better equipped with the health-care and technologic infrastructure to deliver innovative medical technologies. On demographics, it asks in which markets the capacity for innovation and the advancement of medical technology is greatest. And on markets, the survey might ask which countries have the most attractive market opportunity for innovative medical technology.

For each of the eight specific focus subjects related to the regulatory environment, access, demographics, and market factors (see Figure 5-1), lists of metrics are being developed. For access to care, for example, metrics could include the number of physicians per capita and the number of clinical trials. For demographics of disease, life expectancy at birth is one metric, and another is access to technology, which refers to the number of Internet users per capita.

The goal is to consolidate all of the information and present it in a usable format. In its analysis, PwC is looking at historical trends and considering the scorecard by dimensions, markets, and future scenarios to develop a technology predictor.

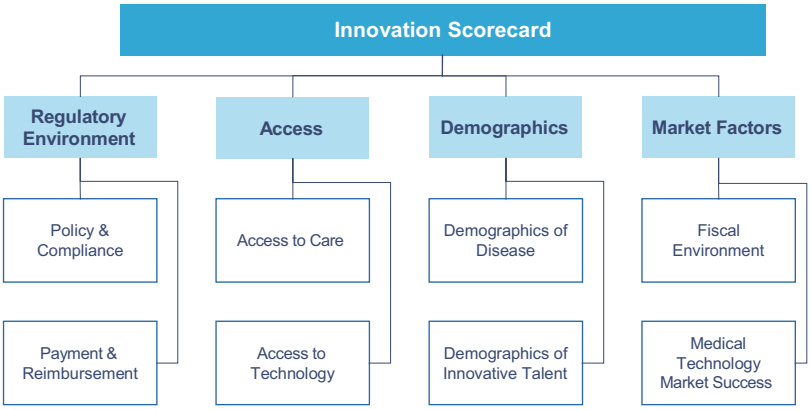

FIGURE 5-1 The PricewaterhouseCoopers innovation scorecard framework.

The findings will be presented in a variety of ways, including "spider charts" or "radar diagrams" for each country. The performance data on the eight subjects will be plotted on a chart, creating a polygon that will allow easy visual comparison of the metrics among countries.

PANEL DISCUSSION: THE GLOBAL REGULATORY ENVIRONMENT

Following the presentations, Jefferys, Trunzo, and Feigal discussed further the favorable outcomes and the challenges of global harmonization, risk-classification issues, other differences between the European and US systems, and concerns during the postmarket period.

Outcomes and Challenges

Feigal noted that when the International Conference on Harmonization (ICH) began to address pharmaceutical harmonization, nearly all countries regulated drugs in some way, but when the GHTF began, 80 countries had no device regulatory scheme whatsoever. The GHTF process was more inclusive than that of the ICH, and its mission included helping countries to develop their medical device regulatory systems. One challenge is to develop systems that are proportional not only to risk but to the resources of the country and of the medical device developers. Another is to build a system that works, in a risk-based way, for thousands of kinds of products. Class II is very broad, ranging from fairly straightforward hospital equipment to complex implants, and the GHTF has taken the stance of trying to separate the higher-risk class II devices from the lower-risk class II devices.

Trunzo concurred, noting that not every country can set up a regulatory system comparable with one used by FDA. Many organizations, such as ASEAN and AHWP, are looking at ways to develop systems that are more streamlined. On the premarket side in many cases, one of the factors that enters into a country's decision to approve a product is whether it has already been approved in a major market, for example, if it has a CE mark or FDA approval. ASEAN is considering a similar approach to that in Europe, using third-party certifications and having a CE-like mark that will allow marketing in all 10 ASEAN countries after one approval.

Those approaches not only move toward harmonization but allow a country to be confident that a product on its market has gone through some kind of regulatory review in a manner that is based on the country's available resources.

Jefferys noted that roughly 750,000 types of devices are on the European market compared with no more than 10,000 active pharmaceuticals. The evidence base is different for devices, and a risk-based approach is ap-

propriate. But one has to remember that although a device may be regarded as being in a lower-risk category, for a variety of reasons, including user issues, the risks may still be great. Therefore, the European legislation makes it clear that the same degree of testing and the same requirements for clinical data are present, although for some the emphasis shifts from premarket regulation to postmarket surveillance.

With regard to combination products, Trunzo noted that the GHTF has established an ad hoc working group to look specifically at combination products in which the device constitutes the primary mode of action because that is in the purview of the GHTF. It was recognized, however, that there needs to be outreach to the ICH and others and that common terminology would be helpful. Jefferys noted that there is a coming together between and within the agencies, for example, in the advanced tissue regulation in Europe. Feigal added that the two therapeutic manufacturing cultures are learning from each other.

Feigal supported the notified-body process and said there are consequences of the US government's tendency to want to do everything itself. There is an opportunity, Feigal said, to re-examine available approaches and to take the best from each.

One factor that has to be taken into account more in the case of devices than pharmaceuticals is user error. The important issues are not usually about design but rather about education of users. It is a bigger challenge for regulators than are standards or designs.

Risk Classification

Number of Categories

The present system of three or four risk categories is about right, Jefferys said. Most would agree that there is a class of low-risk (not no-risk, he emphasized, but lower-risk) devices for which registration and self-regulation are appropriate and that there is a class of potentially higher-risk devices. It is the middle that is up for discussion, and Jefferys supported dividing class II devices into two groups, as is done in Europe.

Trunzo said that whether it is a three-class or a four-class system matters less than how the classification system is implemented and how regulator assign a level of regulatory oversight to the risk associated with a particular device. In any class of devices—whether class A, B, C, or D or class IIA or IIB—there will always be variation. The three-class system in the United States works well, she said, and FDA has applied it appropriately.

Another way to think of the question, Feigal said, is that the United States has 1,800 classes because there are 1,800 device types. Risk assessment is performed product by product. Once a product is on the market,

there are no annual reports, medical device reporting (MDR) is variable, and manufacturers can make changes without notifying FDA.

Differences Between US and EU Risk-Classification Systems

Class III devices are required to have a full design dossier, which will be fully evaluated; whether it is by a notified body or by FDA, the process is the same, and the postmarket requirements are the same.

For class IIA and IIB in Europe, or class II in the United States, a manufacturer has to have a full design dossier and full quality-review systems. In Europe, there is a targeted quality-review system for class IIA devices; a class IIB device will have a full quality review by a notified body, at whose discretion there is a partial or full evaluation of the design dossier.

Feigel said that the classification processes are more similar than different. The major differences between the United States and Europe pertain to a manufacturer's responsibility to obtain periodic third-party regular certification of manufacturing quality and to meet other kinds of standards.

Trunzo added that the GHTF outlines principles for classifying devices with respect to risk, intended use, and a number of other factors.

Other Differences Between the European and US Systems

In addition to the differences in risk-classification systems, several differences between the US and EU systems were mentioned.

During implementation of the new EU device directives, Jefferys said, there was no grandfather clause. Rather, a manufacturer had up to 5 years to obtain a CE mark for an existing product. That admittedly placed a burden on industry, but a similar approach was taken after implementation of pharmaceuticals legislation, and companies complied in both cases.

Clearance or approval in one market does not necessarily translate to others. It was noted that products that have been cleared by FDA in the United States have been turned down or not taken forward by notified bodies in the EU and vice versa, Jefferys said.

Innovation is taken up much more rapidly in United States than in Europe, partly because of how doctors are trained. The differences in insurance systems also come into play with regard to the uptake of new technology.

Postmarket Reporting

The European system includes timelines for manufacturers to report adverse events for medical devices and penalties that can be leveled if they do not report in a timely manner. Health-care professionals are obliged to

report adverse events and are expected to report immediately. Europe has a no-blame culture, Jefferys said, and people are encouraged to report.

Trunzo added that in the United States, manufacturers are required to report adverse events and malfunctions to FDA and to analyze complaints from the field as part of the quality-management system. In addition, FDA has put into place a sentinel initiative and a signal escalation program whereby the agency analyzes the events that are in the reports database.

A committee member noted that in the United States, health professionals do a small amount of the actual reporting, deferring the task to a ward clerk or other staff who have little information. One of the more successful programs in FDA has been the Medical Product Safety Network (MedSun), in part because risk managers are trained by FDA. Feigal noted that MedSun complements the MDR system. The system recruits risk managers from hospitals and extended-care facilities, such as nursing homes. That gives the agency the ability to query a group of health professionals about an issue. In the United Kingdom, 80–90 percent of adverse-event reports go directly from health providers to the device authority. In the United States, manufacturers collect the information from providers. The MDR system is best at identifying signals that need to be followed up more systematically (these systems do not attempt to determine numerators and denominators). There is no system that will address all the issues, Feigal noted.

With regard to notifiable changes in a device, Jefferys said that in both the United States and Europe, the definition of a reportable change is difficult to determine. In Europe, a company is required to document every small change; a significant change must be reviewed by a notified body, and the design dossier must be updated. But it can be hard to tell which is a minor change and which could result in substantial adverse events.

Trunzo noted that the GHTF documents do not directly address making changes. They focus on the quality-management systems approach to documenting change and control of change.

In many cases, the issue is not postmarket lack of information but what to do with the information, Feigal said. For example, when drug-eluting stents were introduced into the market, cases of thrombosis that resulted in death were reported to the agency within a matter of months. FDA issued a statement that said essentially that it was unclear whether a problem was related to the stents but that deaths had been linked to the products, so adverse events should be reported. Even the agency was not sure what the signals meant. Using the national Medicare database (because the drug-eluting stents have a unique billing code), researchers were able to compare the entire stented population before and after the introduction of the drug-eluting products and to quantify the magnitude of the problem. The problem, it turned out, was discontinuation of platelet drugs after a year, not in-stent thrombosis at the time of insertion.

Whereas pharmacy systems track drugs and drug exposures that can be linked to medical outcomes in pharmacoepidemiology, it is extremely difficult to track devices. They generally are not tracked at the model level or in some cases even identified. From procedure codes in computerized medical-records systems, it will be apparent that a patient has received a hip implant, but tracing it to a specific model or specific manufacturer change is difficult with the current system. Tracking systems are needed not just for the assurance of safety but to find the rare signals that do not appear even in large clinical trials of devices.

Electronic record capture is coming in many countries and will be extremely helpful in this regard, Jefferys said. In some areas, registries are also important in that they they provide both numerators and denominators for analysis.

Feigal noted that FDA has the authority to require studies during the postmarket period, but it is not done very often. That, he said, could be looked at more systematically, specifically to determine types of products in class II that are more likely to need postmarket surveillance.

Ultimately, Feigal said, not all the problems can be solved by tweaking the 510(k) clearance process. There needs to be a systems approach to ensuring safety in a system that includes billing, reporting, and postmarket research.

6

Public Comments

As part of its fact-finding process, the Institute of Medicine (IOM) Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process provided an opportunity for public comments on topics relevant to its task.

Medical Professional Association

A representative of the American Academy of Orthopaedic Surgeons (AAOS), which has more than 17,000 board-certified orthopedic surgeons as members, emphasized the role of surgeons in promoting patient safety through the responsible use of implantable medical devices, reporting of adverse events, and postimplantation reviews of patient outcomes. Failures occur and can have devastating effects on patients, but they rarely happen as the result of a single factor that could have been readily identified through premarket studies. AAOS has confidence in the 510(k) process, its rigorous review, and the use of standards, he said. When there is adherence to well-defined procedures, reviewers are empowered to follow the science to its logical conclusions, and there is compliance with internal protocols, the 510(k) process is a reliable and predictable pathway.

AAOS strongly believes that the current 510(k) process, combined with Food and Drug Administration (FDA) surveillance programs, provides the most favorable balance between benefits and risks. That balance is achieved through the 510(k) process's inherent flexibility, which maximizes the benefits of early access to new technology while minimizing the risks associated with innovation. Products cleared through the 510(k) process harness

incremental improvements in technology as a result of small changes in the iterative design process, increase treatment options for individual patients and their disease phenotypes, and contribute to clinical quality improvement through the use of performance information on improved devices. Thus, the process promotes innovation in support of public health.

Incremental improvements in technology translate into substantial changes for patients, he said. In total knee arthoplasty, for example, there were failures from polyethylene wear due to oxidative degeneration. A Harvard innovation added an antioxidant that stabilizes free radicals and reduces the potential for oxidation. The change was cleared through the 510(k) process and has contributed to the extended life of many total knee implants. For patients, that means fewer revision surgeries and improved quality of life.

With flexibility and regulation comes responsibility. FDA must continually evaluate its performance in assessing risks and benefits and in determining safety and effectiveness. The question should be not whether but how changes should be implemented to maintain FDA's performance while expanding it to accommodate greater volumes of 510(k) submissions. Administrative changes are necessary to ensure that decision-making authority resides with the most qualified people and to prevent interference in the review process that is not grounded in scientific inquiry.

Medical Device Manufacturers

Industry Associations

The Medical Device Manufacturers Association (MDMA) represents more than 200 primarily small to middle-size medical device companies. The companies drive innovation and develop the technologies that improve patient care in the long term and reduce the cost of care. A representative of MDMA said that over 100,000 devices have been cleared via the 510(k) process since 1976, and there have been relatively few adverse events. Although some patients have had suboptimal outcomes, which are not to be overlooked, there is a lack of qualitative and quantitative data to demonstrate a systemic failure. There will always be outliers, but in the absence of hard evidence that suggests a systemic failure, he urged the committee to be cautious in suggesting broad sweeping changes in the system as a whole. He suggested that the FDA recall database would be one repository that could be part of a systematic review. If the data suggest systemic failures or isolated pockets of products that need additional scrutiny, MDMA is willing to address them and to make sure that the appropriate special controls or remedies are in place. But it is necessary for the data to demonstrate that

any proposed recommendations would address whatever underlying issues are identified.

The MDMA representative urged the committee to be sensitive, in formulating its recommendations, to the economic and resource realities of the current innovation environment and to recognize that there is a risk–benefit approach to device development. Some 80 percent of device manufacturers have fewer than 50 employees. If regulatory requirements to bring a device to market cost, for example, $100 million but the potential product market itself is $50 million, that will stem the tide of innovation. User fees are not an answer, he said, and he cautioned against making recommendations that rely on industry funding.

He also noted that it is important to look at products in their total life cycle; review should not be a binary event that ends when products receive clearance. Unique device identification and monitoring systems will allow each device to be tracked over the total life cycle of the product. Databases will contain information on how products perform in the marketplace.

A representative of another industry association, the Advanced Medical Technology Association (AdvaMed), said that the organization believes that the 510(k) clearance process is well designed to assess the safety and effectiveness of low-risk and moderate-risk medical devices whose risks are well understood from experience with similar devices. Although the basic structure of the 510(k) process is sound, there is always room for improvement. AdvaMed has been engaged with FDA and other key stakeholders on ways to improve the clarity and consistency of the process.

Patient safety is the number 1 priority of the medical device technology industry, but any regulatory requirement should balance FDA's dual mission of protecting the public health and facilitating innovations that benefit patients. Since the 510(k) program was created in 1976, it has been based on risk: if a new device presents a risk that is greater than that posed by the predicate device, FDA could find that the newer device is not substantially equivalent, classify it into class III, and require submission of a premarket approval (PMA) application.

Risk assessments apply to both a new device's intended use and its technology. The premarket notification program has worked extremely well for more than 30 years, she said. It has permitted FDA to review, on the average, about 3,500 submissions a year in a reasonably timely fashion and to ensure that products that go to market are safe and effective.

The agency has the legal authority to request as much information, including clinical data, as is necessary to make a premarket notification determination. And FDA alone makes the final decision of whether a medical device can be marketed in the United States.

The safety record for 510(k) devices has been strong, and FDA's substantial postmarket controls have contributed to ensuring that both pre-

market notification and PMA devices meet their clearance and approval specifications and are made in quality systems that require the manufacture of reproducibly safe and effective products.

Attempts to paint the 510(k) process as cursory or fast-track are inaccurate and do not serve the interests of patients, the AdvaMed representative noted. Critics who persist in mischaracterizing the process do not take into account the years that it can take for a manufacturer to compile the data needed for a 510(k) submission. It is common for a 510(k) submission to contain hundreds or thousands of pages of documentation based on bench testing, animal testing, nonclinical tests, tests demonstrating conformity to standards, and whatever other requirements FDA may have.

About a year ago, AdvaMed sent a letter to FDA Commissioner Hamburg and then met with her to discuss three specific recommendations to improve the 510(k) process: prompt resolution of the regulatory status of pre-amendment class III devices, identification of class II devices that had cleared the 510(k) process and might need special requirements, and development of an internal committee to improve the Center for Devices and Radiological Health (CDRH) review process.

In March 2010, AdvaMed submitted comments to FDA in response to a series of agency questions asking for stakeholder feedback on ways to strengthen the 510(k) process. Included in the comments were recommendations to improve 510(k) summaries and the de novo process.

AdvaMed supports FDA's current risk-based approach to medical device regulation as embodied in the 510(k) process, which makes safe and effective products and treatments available without unnecessary delays.

A representative of the Medical Imaging and Technology Alliance (MITA) stressed the overall good safety record of imaging devices compared with other environmental conditions in the health-related field. In 2007, for example, about 30 million magnetic resonance imaging (MRI) scans were performed; in 2006, over 68 million were performed. However, from fiscal year (FY) 2005 to FY 2009, only 890 medical device reports (MDRs) from all causes, most of which did not result in patient injury, resulted from millions of examinations. In comparison, the number of hospital-acquired infections is estimated at 1.7 million per year, which lead to about 99,000 deaths, and medication-related injury is estimated at 1.5 million per year. The risk of radiotherapy-related errors with serious medical consequences was estimated at 50–100 per million courses of treatment. Overall, the safety of imaging devices is quite favorable.

The 510(k) application has several key components, including the device description; intended-use statement; predicate-device comparison; declaration of conformity to performance standards and mechanical and safety standards; general clinical safety and effectiveness; clinical data, if applicable; device hazard analysis; software description; cleaning, disinfec-

tion, and sterilization, if applicable; and labeling and promotional material. Clearly, the 510(k) process does not consist of simply a signed statement that identifies a predicate device. It is data-driven and rigorous.

Safety is a key part of the 510(k) process in terms of standards and regulations. Devices cleared through the 510(k) process require conformity to international product-safety standards. IEC 60601-1 contains general requirements for safety, but there are also standards specifically for safety (for example, 60601-1-3 for radiation safety, 60601-2-33 for MRI, and 60601-2-37 for diagnostic ultrasonography). Safety is part of the 510(k) process in terms of device features (for example, display of fluoroscopic radiation time for fluoroscopy, acoustic output display for ultrasonography devices, and automatic exposure controls and audible signals to indicate duration and termination of exposure to x-rays).

Access to imaging devices is an important part of American health care, the representative from MITA said, and lack of access to imaging devices because of unavailability poses a public-health risk.

A representative of the Institute of Molecular Technologies said that the current 510(k) process has been a useful and effective tool for bringing technologies to the marketplace efficiently, and for provide public-health assurance that devices have been appropriately cleared for the marketplace. There will always be exceptions to any clearance process or review process, no matter how many types of controls are in place, and vigilance is always necessary. However, in the current regulatory system, many innovations that pose only low or moderate risk would fall under the PMA process if it were determined that there were no predicate devices. The representative suggested a risk-based approach to devices that do not clearly have predicate devices. There are two approaches. The first approach would be comparison with a generic device type already regulated through the 510(k) process. The generic device would have associated predicate devices, but not as specific devices that one would be required to compare the new devices with. The new devices would be considered not substantially equivalent (NSE) because of minor differences in intended use or in performance as described to FDA. The new devices would present low or moderate risk. The second approach to the generic device type would be nongeneric devices for which there is no predicate for comparison, but the risk posed is still low to moderate. Here, the representative recommended a risk-based approach to analyze what information would need to be brought forward in a 510(k) application for the technology.

One of the issues with the de novo process is that it requires filing of a 510(k) application with FDA even when it is known that no adequate predicate is available. A filer must wait for FDA to review the submission, perhaps 3–6 months or even longer; get an NSE letter; and then refile a submission to FDA de novo. The participant recommended cutting out

that process, going directly to a submission, and allowing a manufacturer to follow the risk-based approach based on the Global Harmonization Task Force (GHTF) model for assessing risk with the documentation that must be submitted for agency review on the basis of that risk. This would mean submitting the same kind of information that is provided in the de novo process but without having to go through the first step of getting the NSE turndown and then resubmitting information to the agency.

Independent Companies

A representative of a startup ultrasonography company said that in recent years, much impressive ultrasonographic technology has reached clinical users through the 510(k) process. From 2003 through 2008, there were an average of 41 MDRs per year regarding ultrasonography, no class I recalls, and an average of six class II recalls per year. During that time, there were over 100 million ultrasonographic examinations per year, for which well over 100,000 devices were used. That, the participant said, is a good safety record for an important modality that has gone through much innovation. A key part of that success is the FDA guidance document that provided a framework for ultrasonography innovation. The ability to prepare and clear 510(k)s in a reasonably efficient manner has been an important part of medical device innovation. If a device manufacturer is not filing at least one 510(k) every 2 years, it may be falling behind the competition. More important, it means that clinicians have older tools and that changes that are taking place in technology—whether in electronics, software, or signal-processing materials—might not be working their way into the clinical environment as quickly as possible.

A representative of another device company emphasized the process of risk assessment. The international standard, ISO 14971, has a long list of questions regarding risks that manufacturers can consider when developing a new product—for example, What kind of energy does the device put out? What kind of mechanical forces are involved? What kind of human errors can reasonably be expected? What kind of patient interfaces might present issues? She recommended that risk analysis automatically be part of the 510(k) submission. She also drew attention to the European regulatory pathway of clinical evaluation for products that do not have to undergo clinical studies. That encompasses review of the clinical literature for the intended uses of a new product and comparing the new product with existing products.

Academic Considerations

A participant who is a professor, lawyer, and cofounder of a startup medical device company asked the committee to keep in mind three fundamental points when considering revisions of the 510(k) process. First, as one increases regulatory burdens or regulatory pathways, he said, one runs the risk of affecting patient autonomy and physician ability to practice medicine. Off-label use of products is well accepted, and the American Medical Association has a policy statement supporting it. Second, system and structure issues are separate from implementation and administrative issues. Third, there is a lack of systemic data on whether the system is working in a way that provides protection for patients and whether an inordinate number of unsafe products are being allowed onto the market. There is some information on the innovation side but very little on the safety side.

A psychologist who studies human error from a systems perspective spoke about how to reduce the likelihood of error relative to the safety and efficacy of medical devices. The 510(k) process contributes to the perpetuation of error in the use of medical devices, she said. Current data reveal trends and what kinds of errors occur, but data on why errors happen are needed. The 510(k) process focuses on changes in devices, but errors in the design of predicate devices are not resolved. The 510(k) process can be a good instrument, she said, but it needs to address the question of what factors contribute to error.

A representative of the National Research Center for Women & Families raised concerns about studies that are based on the Manufacturer and User Facility Device Experience (MAUDE) database. MAUDE is widely perceived to be underreporting problems, he said. He is conducting a study of class I recalls of devices that caused severe injury or death, and his results show that the vast majority are 510(k)-cleared products. The study is in review, and he will provide it to the committee.

A medical device submission consultant provided the committee with a report in which he identifies two root causes of the current problems in the 510(k) system: lack of a process for determining what data are necessary to demonstrate device safety and effectiveness and the dysfunctional requirement to demonstrate substantial equivalence to a specific, legally marketed predicate device to determine, according to risk, whether a new medical device is in class I, II, or III. Focusing on the latter, he said that the 510(k) risk-classification process leads to many problems. For example, much of the agency's review time is consumed in determining the adequacy of a company's substantial-equivalence justification. In all but the simplest of 510(k) applications, that effort consumes 25 percent or more of reviewers' time. Every minute spent on reviewing the justification is a minute not spent on reviewing the data that prove the safety and effectiveness of a new device.

Once a bad decision is set in a 510(k) predicate history, innovation suffers. Additional factors contribute to the substantial-equivalence issue. For example, what are the distinctions between *intended use* and *indications for use*? How do we properly define *technology*? The substantial-equivalence argument rests on parsing such terms. Industry cannot predict how a reviewer will interpret the terms, because they are not consistently defined or applied. That gives rise to poor or delayed decisions of substantial equivalence, which in turn delay innovation. The 510(k) substantial-equivalence process also creates public-confidence issues. The press has wrongly characterized the substantial-equivalence process as a shortcut for industry or an abbreviated review for the agency.

The solution to the 510(k) substantial-equivalence problem, he said, is for FDA to adopt a truly risk-based classification system that is blind to whether a device is innovative or "me-too." The European and GHTF systems are good examples of well-tested processes for rational risk classification. The IOM committee may need to call for legislation that allows repair of the broken 510(k) risk-classification process. By implementing a modern risk-classification process that has flexibility for continuous improvement, we will increase the agency resources available to review the safety and effectiveness of devices, improve the predictability of the review process, improve public confidence in our work, and begin to restore the environment that fosters innovation for better public health.

Patient-Advocacy Perspectives

The committee heard testimony from representatives of Truth in Medicine Incorporated, a patient-advocacy organization that focuses on educating the public about the potential risks posed by and complications of the implantation of synthetic surgical mesh into the human body. Mesh is used in hernia repair, bladder suspension, and treatment of pelvic-floor disorders. Statements were given by the organization's president and founder, the executive director, and several individual members, all of whom shared their personal experiences with the device. Those participants attended to represent the thousands of others who have had similar adverse experiences with medical mesh products. The organization noted among its accomplishments its successful urging of FDA to issue a public-health notification warning of the serious risk poses by and complications of the transvaginal placement of synthetic surgical mesh. The warning was issued to health-care practitioners in October 2008.

Participants shared their clinical experiences of chronic pain and discomfort, infection, chronic inflammation, incontinence and urinary retention, disability, multiple surgical attempts to remove mesh and address complications, and other illness, which had brought some of them close

to death. Some described having endured over 20 operations in less than 10 years in attempts to remove mesh that had migrated or eroded. Others described the challenge of finding a doctor willing to perform further complicated and risky operations to continue to remove bits of mesh. They candidly described the toll that those health outcomes had taken on their lives, such as the inability to work, loss of employment or personal business, loss of health-insurance coverage, financial ruin, homelessness, and stress on personal relationships, including effects on intimacy with spouses and partners. It was pointed out that additional people had registered to provide comment at the workshop but were unable to attend because of health issues.

Participants explained how mesh systems were cleared by FDA for marketing through the 510(k) process. They expressed concerns that the 510(k) process allows unproven medical devices onto the market, inasmuch as clearance does not require proof of safety or efficacy of class I or class II devices. As a result, they said, an uninformed, unaware public is endangered daily by unsafe and unproven medical devices.

The organization specifically recommended that the committee consider the following changes in the 510(k) clearance process:

- Educate the American public about the difference between premarket approval and premarket notification.
- Make adverse-event reporting mandatory, with clear consequences for silence by doctors, hospitals, and medical device makers.
- Create a specific guide for FDA and CDRH to make better use of their regulatory authority. The decision-making process for when and how to use FDA's regulatory authority should not be left to the discretion of agency employees.
- Include a mechanism which stops medical device makers from paying doctors to use products off-label to increase the sales of their products.

Participants called for expansion of informed consent, making it mandatory, for example, for a medical implant device package insert to be reviewed by the doctor with the patient 3–7 days before surgery (not on the day of surgery or when the package is opened in the operating room). It was also stressed that stakeholder involvement should be a critical component of the 510(k) process. One suggestion was for FDA to meet regularly with patients who have been adversely affected by the process. Participants also said that the 510(k) process should be more transparent.

Appendix A

Workshop Agenda

Hotel Monaco
Paris Ballroom
700 F Street, NW
Washington, DC 20004

Monday, June 14, 2010

8:30 AM	**Welcome and Opening Remarks** David Challoner, *Chair*, IOM Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process
8:50	**Legislative History of the Medical Device Amendments of 1976** Peter Barton Hutt, Covington & Burling, LLP
9:30	**Premarket Notification: A Key Element of US Medical Device Regulation** Philip J. Phillips, PCG, LLC Larry Kessler, University of Washington, School of Public Health (coauthor)
10:10	**Break**
10:30	**FDA's Compliance Infrastructure** Timothy A. Ulatowski, Director, Office of Compliance, Center for Devices and Radiological Health, FDA

11:10 **Structure of the Medical Device Industry Innovation Ecosystem**
Josh Makower, Consulting Associate Professor of Medicine, Stanford University Biodesign Program, and Founder and CEO, ExploraMed Development, LLC

12:00 PM **Lunch**

1:30 **Impact of the Regulatory Framework on Medical Device Development and Innovation**
David W. Feigal, Jr., Vice President, Global Regulatory, Amgen, and Associate Faculty, Arizona State University School of Law

2:10 **Balancing Patient Safety and Innovation Panel Discussion**
Moderated by William Vodra, Committee Member
Panelists:

- Workshop speakers: David W. Feigal, Jr., Peter Barton Hutt, Josh Makower, Philip Phillips, and Tim Ulatowski
- Amy Allina, Program and Policy Director, National Women's Health Network
- D. Bruce Burlington, Independent Consultant
- William Vaughan, Consultant, Consumer's Union

3:00 **Break**

3:15 **Public Comment—Registered Speakers**

5:30 **Recess**

Tuesday, June 15, 2010

8:30 AM **Welcome**
David Challoner, *Chair*, IOM Committee on the Public Health Effectiveness of the FDA 510(k) Clearance Process

8:40 **Comparative Overview of Medical Device Regulatory Systems**
David Jefferys, Senior Vice President, Global Regulatory, Healthcare Policy Department, Eisai Europe Ltd.

9:20	**Past, Present and Future of Global Harmonization** Janet Trunzo, Executive Vice President, Technology & Regulatory Affairs, Advanced Medical Technology Association (AdvaMed)
10:00	**Update on PWC's Medical Innovation Technology Score Card** Doug Mowen,[1] Managing Director, Medical Device Industry Practice, PricewaterhouseCoopers
10:40	**Break**
10:50	**The Global Regulatory Environment Panel Discussion** Moderated by Kathryn Zoon, Committee Member Panelists: • David W. Feigal, Jr., David Jefferys, and Janet Trunzo
11:30	**Public Comment—Registered Speakers**
12:30 PM	**Adjourn**

[1]This presentation was given by Janet Trunzo on behalf of Doug Mowen, who was unexpectedly unable to attend the workshop.

Appendix B

Biographic Information on Invited Speakers, Panelists, and Authors of Commissioned Papers

Amy Allina is the program director of the National Women's Health Network (NWHN), a nonprofit organization based in Washington, DC, that works to improve the health of all women by influencing health policy and supporting informed consumer decision making. She plans and implements the NWHN's policy agenda in its high-priority subjects—reproductive and sexual health, menopause and aging, and access to health care—and represents the NWHN with Congress, the Food and Drug Administration, and the National Institutes of Health. Ms. Allina serves on the Board of Directors for the Guttmacher Institute and the Reproductive Health Technologies Project. Before joining the NWHN in 1999, she worked on women's health issues at the public-policy consulting firm Bass and Howes. She was also previously a political organizer for the Maryland affiliate of NARAL and an associate editor of *Multinational Monitor*, a monthly magazine founded by Ralph Nader. She is a graduate of Harvard University.

D. Bruce Burlington, MD, an infectious-disease internist, is an independent consultant on pharmaceutical-product development and regulatory affairs. He has special interests in helping companies to plan development of their drugs on the basis of Food and Drug Administration (FDA) and European Union requirements, prepare for meetings with FDA and its advisory committees, develop risk-management plans, conduct product due-diligence evaluations, and set up process, organization, and staffing plans to achieve their regulatory obligations.

Dr. Burlington was executive vice president and worldwide head of regulatory affairs, human safety, and quality at Wyeth. He led the company

in the development and US and global registration of many products and in improving Wyeth's compliance posture. He also successfully navigated the company through an FDA consent degree. During those 8 years—as a member of many Wyeth governance councils and committees, including the executive-licensing, capitol-expenditure, and commercial councils—he participated broadly and in depth in analyzing the complex business forces driving industry.

Before joining Wyeth, Dr. Burlington served in FDA for 17 years. He was the first physician named as director at of the Center for Devices and Radiological Health (CDRH), where he led major changes, increased the rigor of clinical investigation of medical devices, and championed innovations in the center's work with industry. Before that, he was a research immunologist and then a manager in the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research (CDER). In those centers, he had responsibility for viral vaccines, investigational biologics, review of biologic license applications, approval of new drug applications, and generic drugs. As medical deputy director in CDER, he also oversaw policy and compliance decisions related to pharmaceuticals.

David W. Feigal, Jr., MD, MPH, is the vice president for global regulatory affairs in Amgen in Thousand Oaks, California. His career in the development of medical therapeutics began with training as a physician epidemiologist with an MD from Stanford University and an MPH from the University of California, Berkeley. He did his internal-medicine residency training at the University of California, Davis and a fellowship in clinical epidemiology at the University of California, San Francisco (UCSF). He joined the UCSF School of Medicine faculty in 1984 with joint appointments in the Department of Medicine and the Department of Epidemiology and Biostatistics and in 1989 moved to the Department of Medicine of the University of California, San Diego.

Dr. Feigal came to the Food and Drug Administration (FDA) in 1992 and headed the Center for Drug Evaluation and Research Antiviral Drug Division, the Anti-Infective Drug Division, and ODE IV. In fall 1997, he moved to the Center for Biologics Evaluation and Research as medical deputy director. In spring 1999, Dr. Feigal became the director of the Center for Devices and Radiological Health (CDRH). At CDRH, he was an advocate for the center's science and education programs and worked with Congress and industry to launch a medical devices user fee. In 2004, he left FDA to join a regulatory consulting group, NDA Partners, LLP, and resume teaching as a faculty associate at the Sandra Day O'Connor Law School of Arizona State University. In 2006, he joined Élan Pharmaceuticals in South San Francisco as senior vice president for global regulatory and global safety

surveillance before moving to Amgen in 2008. In August 2010, he will return to his consulting practice.

Peter Barton Hutt is a senior counsel in the Washington, DC, law firm of Covington & Burling, specializing in food and drug law. He began his law practice with the firm in 1960 and, except for his 4 years in the government, has continued at the firm ever since. From 1971 to 1975, he was chief counsel for the Food and Drug Administration (FDA).

Since 1994, he has taught a full course on food and drug law during winter term at Harvard Law School. He is the coauthor of *Food and Drug Law: Cases and Materials* (Foundation Press) and has published more than 175 book chapters and articles on food and drug law and on health policy.

Mr. Hutt has represented the national trade associations of the food, prescription-drug, nonprescription-drug, dietary-supplement, and cosmetics industries. While at FDA, he drafted the legislation that became the Medical Device Amendments of 1976, and beginning in 1962 he has participated in the drafting of most of the major legislation amending the Federal Food, Drug, and Cosmetic Act. He has testified before the House of Representatives and Senate more than 100 times either as a witness or as counsel accompanying a witness.

Mr. Hutt has been a member of the Institute of Medicine (IOM) since it was formed in 1971. He has served on the IOM Executive Committee and other National Academy of Sciences (NAS) and IOM committees. He recently served on the Science Review Subcommittee of the FDA Science Board to review the FDA science needs to perform its regulatory mission. He serves on a wide variety of academic and scientific advisory boards, on the boards of directors of venture-capital startup companies, and on the advisory boards of six venture-capital firms.

Mr. Hutt has served on the IOM Roundtable for the Development of Drugs and Vaccines Against AIDS, the Advisory Committee to the Director of the National Institutes of Health, the NAS Committee on Research Training in the Biomedical and Behavioral Sciences, the National Institutes of Health Advisory Committee to Review the Guidelines for Recombinant DNA Research, the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS established by the President's Cancer Panel of the National Cancer Institute at the request of President Bush, and five Office of Technology Assessment advisory panels. He was a member of the New Foods Panel of the White House Conference on Food, Nutrition, and Health and wrote the panel report.

In April 2005, Mr. Hutt was presented the Distinguished Alumni Award by FDA. In May 2005, he was given the Lifetime Achievement Award for research advocacy by the Foundation for Biomedical Research.

David Jefferys, BSc, MD, FRCP, FFPM, FRSM, FRAPS, is the senior vice president for global regulatory, health-care policy, and corporate affairs of Eisai Europe and chairman of the Eisai Global Regulatory Council. He also sits as a member of the European Working Group of the United Kingdom (UK) Ministerial Industry Strategy Group and UK Innovation Board. He is chairman of the Association of the British Pharmaceutical Industry Regulatory Affairs Group and a member of several European Federation of Pharmaceutical Industries and Associations committees.

Dr. Jefferys joined Eisai in January 2005 on retirement from the UK civil service. He qualified in medicine in 1976 and after a career in clinical and academic medicines joined the UK Department of Health in 1984 to work on the review of medicines. He rose to become director of the Licensing Division and an executive director of the Medicines Control Agency. During that time he served as the principal assessor for the Committee on the Safety of Medicines. He was also a delegate to the Committee for Proprietary Medicinal Products (CPMP) from 1986 to 1994 and chaired the operations working party of the CPMP (now the Committee for Medicinal Products for Human Use, CHMP). From 1995 to 2000, he was the UK delegate on the CPMP (CHMP). He chaired the Mutual Recognition Facilitation Group and the Pharmaceutical Evaluation Reports Scheme Committee. He was a World Health Organization adviser. During that time, Dr. Jefferys was involved with the International Conference on Harmonisation and joined the CMR International Regulatory Board in 1992, becoming chairman of the Advisory Board from 2000 to 2004. He remains a member of the board.

In February 2000, he was appointed chief executive director of the Medical Devices Agency for the Department of Health. He served on the Medical Device Expert Group of the European Union and on the Global Harmonization Task Force. He was a member of the Healthcare Industry Task Force and chaired its Regulatory and Patient Safety Group. On the creation of the Medicines and healthcare Products Regulatory Agency, he acted as joint chief executive until April 2004, when he transferred to become special adviser in advanced health-care technology to the Department of Health and worked on secondment with the European Medicines Agency on benefit–risk evaluation.

Larry G. Kessler, ScD, is professor and chair of the Department of Health Services of the University of Washington School of Public Health. In that role, he directs more than 60 faculty members who provide education in a wide variety of health-services disciplines leading to degrees in public health, including a PhD program, a master's of public health, a master's of health administration, and a recently developed undergraduate major in public health. The department also contains four centers; three are concerned with

different aspects of public-health research, and the fourth is the Northwest Center for Public Health Practice.

Before joining the faculty of the University of Washington, he worked for 30 years in the federal government, first in the National Institute of Mental Health, then in the National Cancer Institute (NCI), and most recently in the US Food and Drug Administration (FDA) Center for Devices and Radiological Health. He obtained his degree in operations research from the Johns Hopkins School of Public Health in 1978.

In September 2002, Dr. Kessler was appointed director of the Office of Science and Technology in FDA's Center for Devices and Radiological Health (CDRH). In that position, he directed the efforts of the laboratories of CDRH and the Standards Coordination Program. The office became the Office of Science and Engineering Laboratories (OSEL) in a reorganization effort designed to integrate science and engineering into the function and mission of CDRH. OSEL plays a crucial role in identifying key scientific questions and solutions concerning device safety and effectiveness.

In June 1995, he joined CDRH as the director of the Office of Surveillance and Biometrics. Under his leadership, the office has implemented the medical device reporting regulation for user reporting, has developed a program for reducing the burden on industry for repetitive reporting, and has completed a pilot program to develop a sentinel system for user-facility reporting of adverse events. In addition, he has helped to develop a new program that encourages the application of a wide variety of new statistical methods, with a focus on Bayesian methods, for the device review process. From 1996 through 2001, he served as chair of Study Group 2 of the Global Harmonization Task Force (GHTF), concentrating on postmarket vigilance and surveillance. Dr. Kessler was chair of the GHTF from 2007 to 2008.

Joshua Makower, MD, MBA, has dedicated his life to the creation of medical technologies that improve patients' quality of life and is the founder and CEO of ExploraMed Development, LLC, a medical device incubator based on the West Coast. He also serves as a consulting associate professor of medicine in Stanford University Medical School and cofounded Stanford's Biodesign Innovation Program. A compendium of the materials created to support the teaching efforts in the Stanford biodesign program has recently been published by Cambridge University Press: *Biodesign: The Process of Innovating Medical Technologies*. Dr. Makower is a venture partner with New Enterprise Associates, where he supports investing activity in the medical device arena. He has founded several companies through the ExploraMed incubator that have achieved successful M&A transactions, including Acclarent, Inc., a company focused on developing novel therapies in ENT, which was acquired by Johnson & Johnson in 2010; TransVascular, Inc., a company focused on the development of a completely catheter-based

coronary-bypass technology, which was acquired by Medtronic, Inc., in 2003; and EndoMatrix, Inc., a company focused on the development of a novel therapy for incontinence and gastrointestinal reflux, which was acquired by C.R. Bard in 1997. Dr. Makower was a founder and until 1995 manager of Pfizer's Strategic Innovation Group, a group chartered to create new medical device technologies and businesses for Pfizer. He serves on the Board of Directors for NeoTract, Inc., Moximed, Inc., Intrinsic Therapeutics, Inc., ExploraMed III, Inc., and Vibrynt, Inc. Dr. Makower holds more than 60 patents for various medical devices in the fields of orthopedics, otorhinolaryngology, cardiology, general surgery, drug delivery, and urology. He holds an MBA from Columbia University, an MD from the New York University School of Medicine, and an SB in mechanical engineering from the Massachusetts Institute of Technology.

Doug Mowen is a managing director in the US Life Sciences advisory practice of PricewaterhouseCoopers. For the last 12 years, he has worked broadly in the medical device industry, including orthopedic, cardiac-rhythm management, and medical equipment companies. His focus has been on commercial compliance, supply and quality operations, patient-management businesses, and customer strategies. Before his current role, he was a partner in KPMG, a managing director of the life-sciences practice in BearingPoint, a marketing manager for the Hewlett-Packard company, and a design engineer for Unisys. Mr. Mowen has a BS in computer science and mathematics from the University of Pittsburgh.

Philip J. Phillips, MBA, is president of Phillips Consulting Group, LLC. He has 28 years of experience in Food and Drug Administration (FDA) regulation of medical devices, having focused on the development and implementation of numerous regulatory strategies regarding the design, manufacture, and marketing of medical devices in the United States. Mr. Phillips has expertise in a wide array of regulatory matters, including FDA jurisdiction, device classification, clinical trials, human-subject protection, and product labeling, promotion, and advertising. His device experience crosses all medical specialties, including in vitro diagnostic devices. He has promulgated regulations and developed numerous guidance documents aimed at clarifying FDA premarket requirements and expectations.

Mr. Phillips has extensive experience in explaining and defending positions before Congress, the Department of Health and Human Services (HHS), FDA and its advisory committees, and other federal agencies. He has represented the US government in negotiations with the European Union and is an authority on dispute resolution and effective interaction with FDA and related agencies. Also recognized as an authority in device regulation,

he has served as an expert witness in court proceedings and is a frequently invited speaker at scientific and regulatory forums.

He has received numerous HHS, FDA, and Center for Devices and Radiological Health (CDRH) awards, including two HHS Distinguished Service Awards and three FDA Awards of Merit.

During his 24-year FDA tenure, Mr. Phillips streamlined medical device review processes and launched numerous agency initiatives aimed at enhancing public health while lessening regulatory burden. In addition to serving as the Office of Device Evaluation deputy director for science and regulatory policy, he served as director of program operations, interim director for the Division of General and Restorative Devices, deputy director for the Division of Ophthalmic Devices, and chief of the Diagnostic and Surgical Devices Branch.

Mr. Phillips began his FDA career as an interdisciplinary scientist. He holds a bachelor's degree in microbiology from the University of Maryland and an MBA from the George Washington University. He also completed the George Washington University Contemporary Executive Development Program.

Janet E. Trunzo, MS, is executive vice president, technology and regulatory affairs, of the Advanced Medical Technology Association (AdvaMed). During her tenure at AdvaMed, she has focused on the passage of the Medical Device User Fee and Modernization Act of 2002 (MDUFMA) and led the industry effort in negotiations with the Food and Drug Administration on the reauthorization of MDUFMA, which was enacted in September 2007. She also concentrates on regulatory harmonization in global economies, including those of Japan and China. Ms. Trunzo represents the US device industry on the Global Harmonization Task Force and just completed her term as vice chair of its Steering Committee. She is a member of the Board of Trustees of the international Global Medical Device Nomenclature Agency. Before joining AdvaMed, Ms. Trunzo held positions at Hybritech, Inc., a medical device and diagnostics manufacturer, and Scripps Clinic and Research Foundation, a hospital, diagnostic clinic, and research institute. Ms. Trunzo received her MS in health physics from Rutgers University and her BS in Chemistry from California State College.

Timothy A. Ulatowski is the director of the Office of Compliance of the Food and Drug Administration (FDA) Center for Devices and Radiological Health. He manages four divisions tasked with promoting consumer health and safety, promoting compliance and product quality, and enforcing the medical device and radiologic-health laws and regulations. Mr. Ulatowski has been with FDA since 1974 and with the Office of Compliance since January 2003. Before his position in compliance he was a division director in

the Office of Device Evaluation and was active in domestic and international standards development. He was until recently the head of the US delegation to the Global Harmonization Task Force. Mr. Ulatowski holds undergraduate and graduate degrees in microbiology and biomedical engineering.

William Vaughan is a consultant to Consumers Union on Food and Drug Administration issues. Starting in 1965, he worked for various members of the US House of Representatives Committee on Ways and Means. He retired in 2001 as staff director for the minority on the Subcommittee on Health. He worked as a lobbyist for Families USA from 2003 to 2005 and has been a senior health-policy analyst with Consumers Union, the independent, nonprofit publisher of *Consumer Reports*, from 2005 to February 2008 and from February to December 2009. He is a member of the board of the National Committee to Preserve Social Security and Medicare and a policy adviser to the Medicare Rights Center.

Appendix C

Premarket Notification: A Key Element of US Medical Device Regulation

Larry Kessler, ScD, and Philip J. Phillips, MBA

EXECUTIVE SUMMARY

The regulation of medical devices in the United States is a complex system of interwoven requirements that are intended to be applied to industry based on the nature of particular devices that it makes and the degree of protection that is needed to provide the American public with reasonable assurance of safety and effectiveness. The main framework for this system is a classification scheme that dictates the overall approach to be taken to accomplish this goal.

Section 510(k) of the Federal Food, Drug, and Cosmetic Act (the act) is but one of many controls that contribute to ensuring that medical devices that are used in the United States are among the safest and most effective in the world. While the US Food and Drug Administration (FDA) premarket review system may not be perfect, it represents a system that is at least as stringent as anywhere in the world. Coupled with the most extensive and utilized postmarket reporting system in the world, dangerous products do not make it to market or are identified and removed soon after distribution begins. Although Section 510(k) was initially intended to be the principal means by which new medical devices were classified, the 510(k) program has evolved in an effort to meet the challenges of a diverse and rapidly changing industry and a highly scrutinized regulatory agency that has never been provided with the necessary resources to meet everyone's expectations.

Today's 510(k) program is the result of a conscious effort to provide reasonable regulation in light of the agency's inability to develop mandatory performance standards for class II medical devices and inadequate FDA resources to withstand any appreciable shift in the numbers of new

medical devices that are subject to premarket approval requirements. Plagued with vague concepts such as substantial equivalence, intended use and predicate devices, the program is particularly vulnerable to intermittent inconsistencies in how each concept is interpreted and applied in agency decision-making, as well as misunderstanding by stakeholders that monitor FDA activity. Coupled with the fact that all medical devices are subject to eventual failure, and failure rates are among the most challenging data to understand, demand for regulatory reform is not unexpected. While the US system for regulating devices can certainly be improved, any attempt to reform the 510(k) program should be based on reality, not perception, and a clear understanding of how the components of the entire regulatory system interrelate and contribute to the overall goal of protecting and promoting public health.

In summary, any regulatory framework will have strengths and weaknesses and this applies to the 510(k) program and the rest of the regulatory structure at FDA's Center for Devices and Radiological Health (CDRH). We show the 510(k) review program's strengths and weaknesses and suggest important areas for consideration to improve the current system. Should an entire overhaul of the system be attempted, we provide information that may be useful in creating a new regulatory structure and process.

OVERVIEW OF US MEDICAL DEVICE REGULATION

FDA is responsible for protecting the public health by ensuring the safety, effectiveness, and security of human and veterinary drugs, biological products, medical devices, foods, cosmetics, and products that emit radiation. The agency is also responsible for promoting the public health by helping to speed innovations that make medicines, medical devices, foods, and radiation-emitting products safer, more effective, and more affordable; and helping the public to obtain accurate, science-based information necessary to use medicines, medical devices, foods, and radiation-emitting products to safeguard their health.[1] Recently, FDA was given the authority to regulate tobacco products.

In the context of medical device regulation, the word device is defined by Section 201(h) of the act as follows:

The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or

[1]Refer to FDA mission statement available at http://www.fda.gov/aboutfda/whatwedo/default.htm.

other similar or related article, including any component, part, or accessory, which is—

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in 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 its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.

Simply stated, a device is virtually any health-care product that fulfills its intended purpose by physical and/or mechanical means, rather than through chemical and/or metabolic activity. Although the mechanism of action may be chemical in nature, in vitro diagnostic (IVD) products also fit the definition of medical device. The breadth of products regulated as medical devices is tremendous; ranging from simple tongue depressors, bandages and gauze to complex implantable cardiac defibrillators, intraocular implants and DNA probes. To complicate matters, device components and accessories are also devices regulated by FDA. Most stakeholders, including health-care providers, consumers, and even members of Congress, have little appreciation for the breadth and diversity of medical devices regulated by the agency.

FDA ensures that medical devices are safe and effective, under the authority granted by the act and in accordance with the implementing regulations found principally in Title 21 of the *Code of Federal Regulations* (CFR), Parts 800 through 1299. CDRH is the organizational component primarily responsible for ensuring that medical devices are safe and effective. A few medical devices are regulated by the Center for Biologics Evaluation and Research (CBER), including medical devices related to licensed blood and cellular products, while a small, but growing number of devices are combined with drugs and biologics (referred to as combination products) that are regulated by the FDA center with responsibility over the product's primary mode of action.

Medical devices are regulated by FDA through a classification system. While classification is commonly described as a risk-based system, this is an oversimplification. A device's classification is actually based on (1) the risk(s) posed by the product, (2) the available knowledge related to the product's intended use and technology, and (3) the level of regulatory control needed to adequately ensure safety and effectiveness.

The objective of FDA device regulation is to provide the American

public with a *reasonable assurance of the safety and effectiveness* for all medical devices (21 USC § 393(b)). The basic framework for achieving this objective rests on a classification system in which a particular device's class designation dictates the applicable regulatory requirements. FDA's approach to ensuring safety and effectiveness depends upon the class of the device, and varies with the level of concern that FDA has regarding the adequacy of existing controls to provide this assurance.

The act defines three classes of medical devices: class I, class II, and class III. Class I devices are simple products that usually present minimal potential for harm to the user. These devices are subject to "general controls", a set of controls applicable to virtually all devices that involve substantive regulation by FDA. General controls include labeling requirements, provisions against adulteration and misbranding, good manufacturing practices (GMPs), establishment registration, medical device listing, medical device reporting and premarket notification ("510(k)") prior to marketing a device. FDA has since exempted most class I devices from 510(k) requirements in implementing the FDA Modernization Act of 1997 (FDAMA 97).

In general, class II devices present a greater level of potential risk than class I devices, but their safety and effectiveness can be ensured through a combination of general controls and additional regulatory requirements designed to mitigate the risks of concern that are associated with the particular device type. All class II devices should be subject to additional special controls to ensure their safety and effectiveness. Special controls include specific labeling requirements, mandatory performance standards, postmarket surveillance, patient registries, guidelines (such as for providing clinical data in 510(k) submissions), recommendations, or virtually any other actions that the agency determines are necessary to ensure safety and effectiveness.[2] By establishing special controls through notice and comment rule-making, FDA establishes a degree of enforceability. Despite the benefits of special controls, they have only been established on a case by case basis for select class II devices, most frequently associated with classification or reclassification actions after enactment of the Safe Medical Devices Act of 1990 (SMDA 90).

Under US law, class III devices support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury to patients. It is on this basis that class III devices are subject to the highest levels of FDA's regulation, including general controls and any relevant performance standards and special controls, and a "device-by-device" demonstration of safety and effectiveness through a regulatory process known as premarket approval (PMA). All new devices are class III by operation of law unless FDA (1) determines the new

[2]Refer to Section 513(a)(1)(B) of the FDCA.

device to be substantially equivalent (SE) to a device previously classified in class I or class II, (2) grants a risk-based ("de novo") classification request, or (3) reclassifies the device into class I or II.[3]

THE EUROPEAN UNION SYSTEM OF DEVICE REGULATION

The European Union (EU) has adopted a very different paradigm than substantial equivalence. The use of "essential principles" that devices must meet before placement on the EU market does not depend on comparing to products on the market nor on any mechanism related to how those products entered EU commerce. Each product must stand independently and have documentation verifying compliance with the essential principles.

The essential principles ensure the safety and performance of medical devices by establishing minimum requirements that all devices must meet. We note that the EU uses the term *performance* rather than *effectiveness*. The expectation in the EU is that a manufacturer designs a product for a certain functional use and that the device then can be demonstrated to *perform* in the manner so designed. For example, if a trocar is intended to puncture flesh in order to gain access to a body cavity, then the essential principles would require a degree of sharpness and stiffness in order to perform this function. How this product is used and whether it has "clinical utility" is not an explicit part of the principles of safety and performance. The clinical use and whether an EU country then includes this device in its "formulary" is a decision taken separately by organizations that are charged with technology assessment and purchasing for these nationalized systems.

With respect to safety, the principles ensure that products are safe when used as intended. Although similar to the 510(k) system, the EU approach is somewhat different. In the EU system, the safety of a product is ensured by meeting the principles that describe whether the product would have any untoward effects on patients.

In addition, the EU also requires that the solutions adopted by the manufacturer for the design and manufacture of the devices should conform to safety principles, taking account of the generally acknowledged state of the art. When risk reduction is required, the manufacturer should control the risk(s) so that the residual risk(s) associated with each hazard is judged acceptable. The manufacturer should apply the following principles in the priority order listed:

[3]A diminishing number of preamendment class III devices remain subject to 510(k) review. This weakness in the regulatory process was recently pointed out in a General Accounting Office report titled *Medical Devices—Shortcomings in FDA's Premarket Review, Postmarket Surveillance, and Inspections of Device Manufacturing Establishments*. FDA is in the process of rectifying this irregularity. It is on this basis that the review of preamendment class III devices is not the focus of this paper.

- Identify known or foreseeable hazards and estimate the associated risks arising from the intended use and foreseeable misuse.
- Eliminate risks as far as reasonably practicable through inherently safe design and manufacture.
- Reduce as far as is reasonably practicable the remaining risks by taking adequate protection measures, including alarms.
- Inform users of any residual risks.

Note the expectation that safety should be a function of the generally acknowledged state of the art, which changes as scientific knowledge changes. A 2007 revision of the directive in the EU placed considerable emphasis on clinical data and the necessity of keeping it up to date via postmarket surveillance in order to confirm the continued acceptability of the benefit:risk ratio. This links back to the current "state of the art." As with everything pertaining to placing on the market in the EU system, this is the manufacturer's responsibility and is constant across all classes of devices. The expectation is that the organizations that audit manufacturers and provide the CE mark (the notified bodies accredited by each EU government) will update their auditing procedures with changes in science. There is no literature based documentation that this has happened, per se.

THE GLOBAL HARMONIZATION TASK FORCE

The Global Harmonization Task Force (GHTF) was established in 1992 as a joint venture between regulatory bodies and medical device trade organizations of Australia, Canada, the European Union, Japan, and the United States. The aim of the GHTF is to harmonize the regulatory systems around the globe in order to

- Reduce redundant efforts regarding placing products on the market.
- Ensure the safety of devices both by having a consistent set of safety principles and adverse event reporting and by sharing such information globally.
- Facilitate international trade of medical devices.

The GHTF is organized around study groups that have written over 30 guidance documents that, when adopted by GHTF partners, will bridge the different regulatory systems. The area of market entry has proved quite challenging. For example, much of the world uses a four class system for devices, whereas the United States uses a three class system. While one can create a map of requirements from one system and class to another, differences remain.

The essential principles adopted in the GHTF (reference SG1/N41R9:2005) are modified from the EU but follow along the same lines. These principles fall in the following categories:

- General requirements.
- Design and manufacturing requirements:[4]
  - Chemical, physical, and biological properties.
  - Infection and microbial contamination.
  - Manufacturing and environmental properties.
  - Devices with a diagnostic or measuring function.
  - Protection against radiation.
- Requirements for medical devices connected to or equipped with an energy source.
- Protection against mechanical risks.
- Protection against the risks posed to the patient by supplied energy or substances.
- Protection against the risks to the patient for devices for self-testing or self-administration.
- Information supplied by the manufacturer.
- Performance evaluation including, where appropriate, clinical evaluation.

Could the current system of 510(k) be modified using regulations and not legal changes to bring products into the US system that have satisfied the essential principles? There are two ways this could occur. The Summary Technical Document (STED) developed by Study Group 1 of the GHTF, assigned the scope of premarket considerations, provides one such avenue. The document includes data demonstrating conformance to the essential principles. If a company wished to bring on a device and did not have a suitable predicate, then the agency could declare the device as nonsubstantially equivalent and request a 510(k) de novo application. The company could elect to submit a STED.

CDRH has encouraged medical device manufacturers to participate in the STED pilot program. Manufacturers would benefit from exposure to the STED preparation process, especially those seeking international regulatory approval or clearance for their devices. In addition, greater industry participation in this program would increase CDRH's familiarity with STED submissions and would allow CDRH to provide constructive feedback to the

[4]The GHTF established a workgroup in 2007 to assess whether its guidance documents would address issues regarding safety and effectiveness with respect to computer software that were devices or operated devices. This workgroup made recommendations to the study groups to make modifications to documents for these issues and these have been resolved in revisions to study group documents.

GHTF on the current STED format. Even more can be done in this regard, and with constrained resources at FDA, all parties should seriously consider how to best use the work accomplished by the GHTF to mutually leverage the world's available resources. This is a true opportunity to improve the entire regulatory process throughout the total product life cycle.

An alternative is to make substantially greater use of international standards and the abbreviated 510(k) submission, wherein a company represents issues of the safety and effectiveness of the device via complying with the essential principles (and completing a STED document) and submits that via the 510(k) abbreviated pathway. In an abbreviated 510(k) submission, manufacturers elect to provide summary reports on the use of guidance documents and/or special controls or declarations of conformity to recognized standards to expedite the review of a submission.[5]

US DEVICE CLASSIFICATION PROCESSES

After May 28, 1976, the enactment date of the Medical Device Amendments of 1976 (MDA 76), FDA made a significant effort to group all medical devices in existence at the time, commonly referred to as preamendment devices, into generic device types with each *generic type of device* being "a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness."[6] Each generic device type was then further categorized by medical specialty and referred to the appropriate classification panel(s) comprising independent experts, principally within the medical specialty. At the time there were 16 classification panels convened exclusively for the purpose of identifying device types' proper classification. As guidance for formulating their recommendations to FDA, the panels answered a specific series of questions prepared by the agency, the *Classification Questionnaire*.[7] The recommendations and the responses to the questionnaire aided FDA in determining the proper classification for each generic device type. The final classification of each generic device type followed notice and comment rule-making and the promulgation of over 1,700 classification regulations. Since the early years, FDA has on occasion encountered additional preamendment devices that escaped the

[5]Refer to *How to Prepare Abbreviated 510(k)* at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134574.htm.

[6]Refer to 21 CFR 860.3(i).

[7]Refer to *General Device Classification Questionnaire* at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080858.pdf.

initial classification and has subsequently classified them through the same process using the current advisory committee structure.

The work of the original classification panels, and the agency actions that followed, form the foundation of the 510(k) program. As new (postamendments) devices prepare to enter the marketplace, with few exceptions, they have been the subject of 510(k) submissions and have demonstrated SE to legally marketed class I and II devices. In fact, FDA has indicated that there have been over 300,000 510(k) clearances in the history of the 510(k) program.

Immediately following enactment of MDA 76, SE to preamendment devices was routinely demonstrated as preamendment devices were the only devices that were available for comparison. Over time, the pool of legally marketed devices expanded with every 510(k) clearance, as did intended uses and technologies. The constant progression within the industry led to SE to recently cleared (postamendment) devices increasingly being demonstrated. In essence, the medical device industry came to quickly realize that there was a greater likelihood of their new devices' being cleared if they were compared to legally marketed devices with similar intended uses and technological characteristics. While comparison to pre-1976 devices is not precluded, such comparisons in today's 510(k) program are unusual. This evolution in the 510(k) program is often dismissed by critics of the program.

Illustration 1 Surgical mesh.

Prior to May 28, 1976, metallic and polymeric screens were in commercial distribution to reinforce soft tissue or bone where weakness exists. These metallic and polymeric screens were categorized by the agency as surgical mesh. As part of the classification process this generic type of device was referred to three classification panels for review and recommendation: the Orthopedic Devices Panel, the General and Plastic Surgical Devices Panel and the Gastroenterology–Urology Devices Panel. All three panels recommended that this generic type of device be regulated in class II subject to performance standards. FDA accepted the panels' recommendations and classified surgical mesh as follows:

Sec. 878.3300 Surgical mesh

(a) *Identification.* Surgical mesh is a metallic or polymeric screen intended to be implanted to reinforce soft tissue or bone where weakness exists. Examples of surgical mesh are metallic and polymeric mesh for hernia repair, and acetabular and cement restrictor mesh used during orthopedic surgery.

(b) *Classification.* Class II

Over the last 34 years, FDA has cleared 547 510(k)s for surgical mesh devices. The clearances span nine product codes[8] and cross virtually all medical specialties. Today's surgical mesh has evolved to include some of the latest absorbable biomaterials. The agency has not given priority to developing performance standards or special controls for this generic type of device.

Just as knowledge and experience influenced the initial classifications, information derived from experience with class III devices has paved the way for occasional reclassification actions. With the passage of time and an accumulation of experience, FDA has gained confidence that some class III device types can be safe and effective and that lesser FDA regulation will continue to ensure their safety and effectiveness. In essence, devices with uses or designs that were once thought to warrant their being subject to class III regulation and the rigors of PMA no longer require such regulation. The flow of devices from class III to class I or II was an anticipated outcome of FDA's device regulatory system that has not been fully realized. Reclassification actions must be based on information in the public domain and significant legal impediments exist that preclude the use of data and information in PMAs for reclassification purposes. Furthermore, resistance by companies that have successfully navigated the PMA process and benefit from the significant barrier to competition that PMA affords and a lack of FDA incentive to pursue reclassification have rendered this less than a successful means to adjust device classification over time.

[8]A product code is a distinct three-letter code that is assigned by FDA at the time of clearance based on attributes of interest to the agency that are associated with the new device as it is included within an existing generic type of device. Product codes serve an administrative function allowing easy identification of devices with the attributes of interest within a generic device type.

Illustration 2 Extracorporeal shock wave lithotripters.

Prior to May 28, 1976, mechanical devices were in commercial distribution that were inserted into the urinary bladder through the urethra to grasp and crush bladder stones. These preamendment medical devices were considered part of a generic type of device referred to as mechanical lithotripters. Following enactment of MDA, the Gastroenterology and Urology Devices Panel recommended that mechanical lithotripters be regulated in class II subject to performance standards. FDA accepted the panel's recommendation and classified the generic type of device under 21 CFR 876.4500. The classification regulation describes the generic type of device as "a device with steel jaws that is inserted into the urinary bladder through the urethra to grasp and crush bladder stones." Performance standards and special controls were never developed for mechanical lithotripters.

When the postamendment extracorporeal shock wave lithotripter, designed to use focused ultrasound to noninvasively fragment urinary calculi within the kidney or ureter, emerged in the middle 1980s, FDA did not find the device SE to the mechanical lithotripter. Based on differences in use and design, as well as different safety and effectiveness questions raised with the use of the new technology, FDA decided that this new device warranted the rigors of PMA. Over the next few years, clinical studies were conducted and PMA applications were eventually submitted and approved. Over time, postmarket experience with the FDA approved devices appeared in the public domain allowing the agency to reclassify extracorporeal shock wave lithotripters into class II subject to special controls (21 CFR 876.5990). Interestingly, the same technology for use in crushing gallstones remains in class III subject to PMA requirements.

Since enactment of FDAMA in 1997, devices determined to be not substantially equivalent (NSE) to legally marketed class I or II devices no longer have to face the rigors of PMA in all cases. The statutory provision, referred to as de novo classification, allows companies that receive NSE decisions to request that their devices be regulated in class I or II and allows FDA an opportunity to avoid unnecessary class III regulation. To date, there have been 55 de novo classifications that have been granted creating the same number of new generic device types.

Illustration 3 Ovarian adnexal mass assessment score test system.[9]

When Vermillion, Inc. wanted to market its OVA1™ Test as a diagnostic, there were no legally marketed devices to which the OVA1 Test could be compared. The OVA1 Test consisted of software, instruments, assays, and reagents all used to obtain the OVA1 Test result. The new device raised issues of intended use and technology that precluded a finding of SE. Although the OVA1 Test could not be found SE, FDA determined that the safety and effectiveness of the device could be ensured when regulated in class II subject to special controls. On this basis, FDA granted a de novo classification request and promulgated the following classification regulation:

21 CFR 866.6050 Ovarian adnexal mass assessment score test system.

An ovarian/adnexal mass assessment test is a device that measures one or more proteins in serum. It yields a single result for the likelihood that an adnexal pelvic mass in a woman, for whom surgery is planned, is malignant. The test is for adjunctive use, in the context of a negative primary clinical and radiological evaluation, to augment the identification of patients whose gynecologic surgery requires oncology expertise and resources.

Further, in addition to the general controls of the Act, the Office of In Vitro Diagnostic Device Evaluation and Safety developed the following special controls:

1. "Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System," which includes recommendations for performance validation and labeling;
2. sale, distribution, and use in accordance with the prescription device requirements in 21 C.F.R. 801.109; and
3. placement of warning statements that address the risks identified in the special controls guidance document in a black box.

TODAY'S PREMARKET NOTIFICATION PROCESS

At least 90 days before marketing a device in the United States for the first time, a manufacturer must notify FDA of its intent and obtain FDA authorization to do so. Furthermore, changing a legally marketed device's design or intended use may render the device to be a "new" device, thereby requiring FDA authorization before the modified device is marketed in the United States for the first time. The agency has regulations that apply

[9]Refer to 510(k) Number K081754 at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=28197.

to changes to legally marketed devices and has issued guidance to clarify requirements.

The objectives of the 510(k) program have evolved over time and are often the subject of debate among interested parties whose understanding of the program varies and whose expectations are not aligned. Initially, the congressional intent underlying the program was very simple; Section 510(k) was a means of classifying new devices, thereby ensuring that they were subject to an appropriate level of FDA regulation sufficient to ensure their safety and effectiveness. With the understanding that a new device found SE to (1) a class I device would be subject to general controls, (2) a class II device would be subject to general controls and the associated mandatory performance standards, and (3) a preamendment class III device would eventually be subject to PMA and that all NSE devices were automatically placed in class III, immediately subject to PMA, 510(k) was merely the means of ensuring that new devices are subject to appropriate FDA regulatory requirements. What this simplistic view did not consider was the rapidly evolving nature of the device industry, FDA's inability to develop mandatory performance standards and the resource demands of PMA. Soon after enactment it became apparent that Congress's initial vision for the program could not be fulfilled; in particular, the agency could not promulgate mandatory performance standards. This prompted the agency to develop program guidance to standardize 510(k) review and identify the key points to consider in determining SE (FDA, 1986). To a large degree, FDA's guidance on the 510(k) program was accepted by Congress and codified in SMDA 90 and its implementing regulations.

From purely an industry perspective, 510(k) most often represents the desirable and most straightforward pathway to market. Yet, for many companies, specification developers and entrepreneurs, 510(k) is a means to elicit financial interest in new products. More specifically stated, 510(k) clearance is a commercially valuable event and often signals an investment opportunity, if only as a platform on which a more commercially appealing device can be built. While we do not know the number of 510(k) cleared devices that never go to market, we know that not all 510(k) cleared devices do and that there are often delays in market entry that are attributable to non-FDA related barriers to market entry.

Among the critics of the 510(k) program, there is a tendency to focus on specific clearances that are often associated with postmarket problems and attribute the observed problems to inadequacies in 510(k) review, thereby concluding that the objectives for the program are not being realized. As a generalization, program critics believe that there are too many new devices escaping PMA requirements and that the criteria for determining SE are skewed in a direction of inadequate public health protection. Of note is the fact that even the occasional critics of 510(k) decision-making appreciate the

concept of regulation based on device classification and do not argue that the 510(k) program is not largely fulfilling Congress's intent.[10]

THE CONCEPT OF SUBSTANTIAL EQUIVALENCE

Between 1976 and 1986, *substantial equivalence* was not defined. In fact, the only guidance bearing directly on the issue of SE can be found in the Report of the Committee on Interstate and Foreign Commerce on the Medical Device Amendments of 1976 (Senate report) which offers the following unhelpful remark:

> The committee believes that the term, substantial equivalence, should be construed narrowly where necessary to assure the safety and effectiveness of a device but not narrowly where differences between a new device and a marketed device do not relate to safety and effectiveness.

Despite the ambiguous nature of the words, during the very early years, determining SE was not a significant challenge for the agency as the magnitude and rapidity of change in use and design were not fully apparent, that is, devices that were the subject of 510(k) submissions did not initially differ appreciably from their preamendment counterparts. Because of the medical device industry's desire for continuous improvement, the need to differentiate new devices from existing ones and the demands of a healthcare system for newer technology; it did not take long for the concept of SE to be challenged by the nature and degree of the change that was occurring, thus creating confusion in FDA and industry and a need for guidance. To complicate matters further, finding a new device NSE challenged FDA's limited resources creating pressure to make Section 510(k) accommodate the majority of new devices entering the marketplace. To a large extent, the first decade of experience with implementing MDA 76 shaped the 510(k) program into the system that it is today, that is, a regulatory system that subjects new devices to appropriate preclinical and clinical testing and high risk devices that warrant class III regulation to the rigors of PMA. While the tendency is to judge the performance of the 510(k) program by the percentages of SE and NSE decisions, this approach ignores the percentage of devices that are withdrawn by their submitters before FDA renders a classification decision. The reason for withdrawals may vary, but many 510(k) submitters simply cannot perform the testing that is required for clearance or the testing is not supportive of a clearance decision.

[10]Medical Devices: Are Current Regulations Doing Enough for Patients? Testimony of Peter Lurie, MD, MPH, and Jonas Hines, Health Research Group at Public Citizen before the US House of Representatives Committee on Energy and Commerce Subcommittee on Health, June 18, 2009.

SE is always approached in the context of comparing a new device to at least one legally marketed class I or II device, referred to as a predicate device. In accordance with Section 513(i) of the act, a medical device is SE to a predicate device if it has the same intended use as the predicate device; and (1) it has the same technological characteristics as the predicate device or (2) it has different technological characteristics which do not raise new questions of safety and effectiveness and is shown to be "as safe and effective" as the predicate device. To fully understand how SE determinations are made, one must understand (1) the concept of "intended use," (2) what constitutes "new questions of safety and effectiveness" and (3) how safety and effectiveness are approached.

INTENDED USE

Intended use is the first consideration when making a SE determination. Despite its importance, it has only been defined in the context of "postmarket" labeling requirements found in 21 CFR 801.4. In this context, the words *intended use* refer to the objective intent of the persons legally responsible for the labeling of devices, intent to be determined by such persons' written or verbal expressions or the circumstances surrounding the distribution of the device. In the context of determining SE, this definition is often cited, contributing to significant confusion. In fact, the agency's use of this definition in the context of 510(k) decision-making led to a change in the law under FDAMA 97 whereby intended use must be determined principally from proposed labeling provided in 510(k) submissions.

The words found in 21 CFR 801.4 are valuable for determining whether a manufacturer is promoting its device for a use other than the use for which the device is cleared, but are problematic for determining SE. Device manufacturers often envision multiple uses for their devices, but may not intend for them to be used for all envisioned uses until evidence can be gathered to support such uses. Some of these uses may be evident from patent materials, as well as the device's design history file, neither of which establish the manufacturer's intent to begin promoting beyond what is described in its 510(k) submission. In hindsight, the agency would have been better off developing a secondary definition of intended use specifically for use in the context of determining SE. In an attempt to define intended use in the 510(k) context, we believe that it may be helpful to initially focus on "indications for use," a primary determinant of intended use that is relatively well understood.

Like *intended use*, the words *indications for use* are not defined in the context of 510(k), however, these words are defined in the context of PMA. According to the PMA procedural regulation, specifically 21 CFR 814.20(b)(3)(i), "indications for use" is a "general description of the dis-

ease or condition the device will diagnose, treat, prevent, cure, or mitigate, including a description of the patient population for which the device is intended." This definition encompasses many indications-for-use statements appearing in labeling for class I and II devices, but overlooks the fact that not all devices require a level of detail in their indications-for-use statements that specifies diseases or conditions, or identifies a patient population. For example, indications for use for many general use devices (for example, scalpels, hypodermic needles and external infusion pumps) include "functional indications for use" that do not provide clinical specificity. Although not defined by regulation, the concept of functional indications for use is evident in labeling for many 510(k) cleared devices and has been advanced through agency guidance. In an October 6, 2005, draft guidance document titled *Functional Indications for Implantable Cardioverter Defibrillators*, FDA defined *functional indications for use* as "an indication statement for a medical device that describes what the device does and does not specify an indicated patient population." As an example, many surgical sutures have indications-for-use statements that only specify that the device is to be used for the approximation of soft tissue, with no reference to specific tissues, anatomical sites or surgical procedures.

While a device's indications-for-use statement represents a large part of a device's intended use for determining SE, intended use in this context also encompasses: who is intended to use the device, where it is intended to be used and under what conditions the device is to be used. To ensure that the 510(k) system functions, each of these factors is constrained to an appropriate level of abstraction that has public health significance. For example, "who" is intended to use a device most often comes down to either a licensed health-care practitioner (prescription use) or a lay user (over-the-counter use); however, on occasion *who* can relate to someone with a minimum level of training or experience, or of a minimum age. In considering "where" a device is to be used, agency consideration most frequently relates to use either in health-care facilities or in the home; however, in some instances the location of use may require greater depth of review. In considering conditions of use, the domain may involve environmental conditions, for example, intended for use in the magnetic resonance imaging field or the number of times that a device is suitable for use (such as, a device that is "single-use" disposable).

In order for a device to be found SE, FDA must find that any differences in intended use between a new device and a predicate do not constitute a "new intended use." In making this decision, the agency exercises considerable discretion and allows changes in intended use where the change does not introduce different types of safety and effectiveness questions compared to the predicate device's generic device type.

To illustrate how the agency has accommodated differences in intended

use to meet changing public health needs, consider in vitro diagnostic devices. In the early years of the medical device program, the vast majority of IVDs were intended for use in hospital or contract service laboratories. Over time, there has been a shift to include physician office laboratories, point of care testing of patients, and lay use in the home. Rather than view any one of these changes as a new intended use worthy of class III status, the agency elected to require data to ensure that new devices function as required in each intended use environment. In so doing, FDA receives the data that it needs for decision-making and avoids the burdens of PMA.

After fully considering FDA's approach to intended use within the confines of the 510(k) program, the concept of intended use as applied to determining SE becomes clearer. In essence, intended use is a regulatory concept that is the first consideration when determining the boundaries of a generic type of device and is most often constructed to encompass the widest breadth of use where the regulatory controls for the generic device type continue to provide reasonable assurance of safety and effectiveness. Again, surgical sutures serve as a simple example.

As previously stated, surgical sutures often carry a very general indication-for-use statement, that is, for the approximation of soft tissue. At the most fundamental level, this indication-for-use statement describes the functional capability of the device and also constitutes the device type's intended use for the purpose of determining SE. Sutures carrying a more precise indication-for-use statement may reference specific tissues or surgical procedures, but are viewed for SE purposes as having the same intended use. It is on that basis that surgical sutures' nonabsorbable poly(ethylene terephthalate) surgical suture is indicated for use "for the approximation of soft tissue such as the repair of meniscal tear injuries."[11]

NEW QUESTIONS OF SAFETY AND EFFECTIVENESS

Under the law, if a device raises "new" questions of safety or effectiveness compared to a predicate device, that is, the new device raises a question that the old device did not raise, the new device cannot be found SE. Given that the detailed content and structure of any question can make it appear dissimilar when compared to questions raised in the past, and therefore "new," FDA loosely interprets the word *new*. As evident in FDA's program guidance to the review staff, the agency interprets "new questions" to be "new types of questions." By inserting the word *types*, different questions can be grouped, thereby providing FDA considerable latitude in deciding what scientific questions justify making a new device NSE.

[11]Refer to 510(k) number K082535 at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=28671.

Advances in materials science provide examples of how specific scientific questions are addressed in the context of SE decision-making. In the medical device industry, manufacturers constantly search for new materials. As new materials are selected for use, questions often arise regarding their suitability for a particular use. While a new use for a material may raise questions, the questions are generally of the same "type" that previous materials have raised and, therefore, rarely justify an NSE decision. In the context of the latest material science, questions regarding a new material's ability to meet the demands of a particular use environment are usually addressed through standard bench and animal testing. The vulnerability of course rests with the fact that in some cases, bench and animal testing reveal no concerns that later appear in actual use conditions. Although postmarket vigilance eventually provides feedback to FDA and the industry so that problems may be addressed, postmarket problems often suggest premarket weakness. Of course, to fully address this perceived premarket weakness, extensive premarket human testing for all new materials or compounds would be needed, thereby taxing FDA's capacity to review products.

Historically, scientific knowledge pertaining to legally marketed class I and II devices has transcended generic device types leading to the appearance of comparisons to multiple devices in a single 510(k) submission. Frequently, devices subject to comparison are inappropriately referred to as predicates even though they may not share a common intended use. The motivation for this practice is efficiency. It often makes scientific sense to consider questions raised during the review of a 510(k) submission in the context of a broader array of legally marketed class I or II devices and not simply a single predicate. There is an obvious relevance to being familiar with the science that has supported a previous 510(k) clearance even if the subject device does not technically qualify as a predicate. An inherent part of today's 510(k) program relies on an ability to answer scientific questions based on past practice. FDA's experience in addressing scientific questions pertaining to any previous 510(k) clearance may support simply answering the question in an effort to avoid an otherwise unnecessary NSE decision. We note parenthetically that this represents a strength of the 510(k) in contrast to the current EU system that does not to allow prior knowledge to enter into decision-making outside of the application of the essential principles. An example of this problem can be found in the 2005 reclassification of orthopedic devices throughout the EU, including hips and knees.[12] While the US FDA can perform such a reclassification device by device, the EU had to perform a "mass reclassification" in order to solve problems it believed it had in only a few devices.

[12]D.F. Williams, The Classification of Total Joint Replacements in the European Union: An Independent Report on the European Commission Proposed Directive for Reclassification of Certain Total Joint Replacement Prostheses, at 44 (October 2003).

Illustration 4 Tepha, Inc.'s TephaFLEX® line of surgical devices.

On November 11, 2005, FDA rendered an NSE decision for the TephaFLEX® Absorbable Surgical Suture (510(k) number K052225). Unlike other legally marketed class II surgical sutures, Tepha's device was made from an absorbable poly(hydroxybutyrate) material comprising an isolate from prokaryotic cells produced by recombinant DNA technology. Rather than pursue PMA approval, Tepha pursued a de novo classification which FDA granted on February 8, 2007. FDA classified the TephaFLEX® Absorbable Surgical Suture in class II (21 CFR 878.4494) and established special controls in the form of a guidance document titled *Class II Special Controls Guidance Document: Absorbable Poly(hydroxybutyrate) Surgical Suture Produced by Recombinant DNA Technology* to address the specific risks to health associated with an absorbable poly(hydroxybutyrate) surgical suture produced by recombinant DNA technology.

Following FDA clearance of its suture, Tepha submitted a 510(k) for a surgical mesh made of its TephaFLEX® material, 510(k) number K070894. Given that the use of this material was as new to surgical mesh as it had been to surgical suture, the material could have resulted in an immediate NSE decision, but it did not. As disclosed in Tepha's 510(k) summary for its mesh, the suture was cited as one of 5 predicate devices and the only predicate that was a suture. While a suture cannot be a predicate device for a surgical mesh due to their different intended uses, comparing the material used in the surgical mesh to the material in the cleared surgical suture represents good science and a proper regulatory decision.

SAFETY AND EFFECTIVENESS

The rules for determining safety and effectiveness are spelled out in regulation. Whether it is classification panels making recommendations to FDA regarding the proper classification of a device or agency employees determining the safety and effectiveness of a new NSE device, the rules are the same. In accordance with 21 CFR 860.7(b), when determining the safety and effectiveness of a device, the following factors are to be considered:

1. The persons for whose use the device is represented or intended.
2. The conditions of use for the device, including conditions of use 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.
4. The reliability of the device.

The same regulation also defines *reasonable assurance of safety and effectiveness*. According to 21 CFR 860.7(d)(1), there is reasonable assurance of safety

> 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.

Likewise, 21 CFR 860.7(e)(1) defines effectiveness as

> when it can be determined, based upon 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.

While the objective of providing a reasonable assurance of safety and effectiveness is the same regardless of the pathway to market, the agency's means of ensuring it is quite different when contrasting class I and II devices with class III devices that are subject to PMA. The safety and effectiveness of class I and II devices is ensured through conformance with the regulatory controls that are associated with a generic type of device and its regulatory class. In the case of class I devices, safety and effectiveness are ensured through the application of general controls. In other words, manufacturers of class I devices that abide by the rules against adulteration and misbranding, register their manufacturing facilities with FDA and disclose ("list") the devices that are being manufactured in each facility, manufacture product under good manufacturing practices, label their devices in accordance with the labeling regulation and report deaths, serious injuries, and malfunctions in accordance with medical device reporting requirements will distribute a product that is reasonably safe and effective for its intended use. Section 510(k) is not applicable to the majority of class I devices making it incumbent upon FDA to monitor industry compliance with applicable requirements through facility inspections and postmarket vigilance. Manufacturers of class I devices, such as patient scales (21 CFR 880.2720), dental drills (21 CFR 872.4130), and nonprescription sunglasses (21 CFR 886.5850) go directly to market with no need for FDA authorization. We note that many of the essential principles are embodied within GMPs, or more precisely the Quality Systems Regulation (QSR). These have been largely harmonized with the EU system and though their application is most often thought of in the compliance or postmarket realm, they are in fact very powerful tools for

ensuring safety and effectiveness of products not only in the United States, but also worldwide. Conformance to quality aspects of manufacturing, which includes a feedback system coupled with corrective and preventive actions, assist in the assurance of device safety.

A particularly important provision of the QSR is known as design controls. The design control provisions of the QSR apply to select class I devices and all class II devices and contribute in significant ways to ensuring device safety and effectiveness, although they are often underappreciated. FDA reserved design controls for products where their application would be necessary to have full confidence in the manufacturer's handling of the product.

For the majority of class II devices, reasonable assurance of safety and effectiveness is provided through the same means as class I devices with two distinctions: (1) most class II devices are subject to 510(k) requirements and (2) all class II devices are supposed to be subject to special controls. The original classification regulations were predicated on FDA's eventually establishing mandatory performance standards for all class II devices. While many devices were placed in class II, FDA's inability to follow through with establishing mandatory performance standards led to legislative change. With enactment of SMDA 90, performance standards were replaced with special controls in the hope that greater flexibility would afford FDA the opportunity to directly and consistently address the risks to health associated with class II devices. While the nature of class II controls has evolved, the basic premise remains: in order for class II devices to be safe and effective, regulatory controls beyond general controls are required. In today's regulatory paradigm, 510(k) attempts to compensate for the lack of mandatory performance standards and special controls with higher expectations and more rigorous premarket evaluation associated with devices in class II. Otherwise, a distinction between class I and II would be nonexistent.

The exact number of class II devices for which FDA has established special controls is unclear and difficult to determine, but the percentage of the total number is small. The only class II devices that have special controls are devices that have been the subject of post-1990 rule-making. In essence, establishing special controls was done when "convenient" for the agency. How does FDA address safety and effectiveness issues relating to class II devices without having mandatory performance standards or special controls? The 510(k) review process compensates for this void through an increasing demand for performance data, including clinical data in select instances, before rendering SE decisions. Basically, 510(k) attempts to ensure the continued safety and effectiveness of each class II generic device type by requiring evidence that the risks associated with new devices are mitigated before they are determined to be part of an existing class.

In discussing FDA's means of ensuring safety and effectiveness for medi-

cal devices, one should avoid comparing 510(k) and PMA as it is technically inappropriate to do so. Premarket approval, as its name implies, is an FDA "approval" that is granted on a device-by-device basis after FDA has determined that the manufacturer has demonstrated that the particular device is reasonably safe and effective. If we turn to 510(k), there is no FDA determination that the device is safe and effective. In fact, referring to an SE determination as an "approval" is prohibited by regulation (21 CFR 807.97). Why does this prohibition exist? Because general controls ensure the safety and effectiveness of class I devices and a combination of general and special controls ensure the safety and effectiveness of class II devices. Section 510(k) is but one of the general controls. By itself, 510(k) is incapable of ensuring safety and effectiveness. As part of the larger regulatory picture, 510(k) contributes to ensuring safety and effectiveness by documenting critical aspects of device performance and through the mitigation of risks. If Congress intends for 510(k) to ensure safety and effectiveness with a "lighter touch" than PMA, then both the regulatory requirements under this section of the act would need to change as would resources to accompany such expectations.

Although 510(k) is a general control, its role in the overall regulatory system has evolved over time. Today, the vast majority of class I devices are exempt from 510(k) as a result of FDAMA 97. This leaves the 510(k) process appearing more similar to a special control than the general control that it is under the law, particularly when one considers that FDA uses the 510(k) process to compensate for the lack of special controls.

If one wants to compare FDA's means of ensuring the safety and effectiveness of class I and II devices with the means used for class III devices, there are similarities and differences (see Table C-1). Under similarities, virtually all medical devices, independent of their regulatory class, are subject to the general controls. How FDA ensures conformance with the general controls differs considerably by regulatory class. For class I and II devices, FDA must decide how to use scarce resources. This results in conformity assessment that is driven by current public health priorities. For all practical purposes, there is little or no relationship between 510(k) and this conformity assessment. This is not the case with PMA. Take conformance with GMPs as an example. For class I and II devices, FDA attempts to conduct manufacturing facility inspections on a biannual basis, though in reality this has been estimated to be on average between 5 and 7 years. This means that it can easily be a minimum of 2 years before FDA visits a manufacturing facility producing 510(k) cleared devices. For class III devices, conformance with GMPs is assessed on a preapproval basis. In other words, before a new class III device is sold in the United States, FDA has visited the manufacturing facility and determined that the facility is operating in conformance with GMP requirements.

THE SCIENTIFIC INTEGRITY OF THE 510(k) PROCESS

The evidence requirements to establish SE vary depending on the class (that is, class I or II), device type, and the issues associated with the new device. For devices that are basically the same as legally marketed devices within the generic device type, the data and information reviewed in support of clearance are primarily descriptive in nature. For new devices in this category, it is not unusual for the review of a 510(k) to focus on the device's intended use and technical specifications. When they are the same, or vary in ways that are not viewed to impact safety and effectiveness, FDA clearance is straightforward. We note that there is some subjectivity in the assessment of such views and this has led to inconsistency in reviews of some types of devices. This is an Achilles' heel of the program and is in contrast to the advantage of a system based on essential principles.

For a new device that differs from devices within the generic type to which it is being compared, the nature and extent of the differences dictate review requirements. In most cases, differences can be categorized as those related to intended use or technology. If a difference relates to intended use and the intended use constitutes a "new" intended use, no amount of scientific evidence will support a finding of SE. In this case, the review of the submission ceases and an NSE decision is promptly issued. If the new device's intended use (1) differs in ways that raise the same types of safety and effectiveness issues as the generic type to which it is being compared and (2) accepted scientific methods exist to answer the question, data are requested for evaluation. The same principles apply to new technology. As long as the technology does not raise new types of safety and effectiveness questions and the questions that are raised can be answered with established scientific methods, the agency usually requests that the submitter provide data. Most often data are from nonclinical studies, but the agency has the authority to require clinical data, if this is the appropriate way to address the question. One must realize that unless FDA's issues are resolved with the type of data or studies that are requested, devices are not cleared for marketing. While FDA requests for data can be challenged, clearances are not forthcoming unless the requested data are provided or the data are determined not to be necessary for clearance.

Changes and Modifications to Legally Marketed Devices

Medical devices have a very short life cycle when one considers the number of changes that a typical device undergoes during the course of a year. Manufacturers often encounter issues with their suppliers, thereby creating a need for alternate sources of raw materials and components, embark on continuous process improvement to enhance manufacturing efficiency, and change or modify their existing product lines to remain competitive and

TABLE C-1 Comprehensive Comparison of the PMA and 510(k) Programs

Comparator	Premarket Approval (PMA)	Premarket Notification (510(k))
Devices eligible for review	Class III	Class I and II[a]
Pathway to US market	Yes	Yes
Alternative pathways to market	Product development protocol (PDP), Reclassification or de novo classification	None
Opportunity for exemption from premarket review	No	Multiple[b]
Evidence required for FDA market authorization	Valid scientific evidence (21 CFR 860.7)	Descriptive and performance data (testing may involve prototypes)
"Least burdensome" provisions of the law apply	Yes—Section 513(a)(3)(D)(ii)—"effectiveness"	Yes—Section 513(i)(1)(D)—"substantial equivalence"
Threshold for FDA market authorization	"Reasonable assurance of safety and effectiveness"	"Substantial equivalence"
Regulatory Difficulties	**Premarket Approval (PMA)**	**Premarket Notification (510(k))**
Program complexity	High	Low to Moderate
Submission preparation complexity	High	Simple
FDA review cost (FY 2005)[c]	$870,000	$18,200
Team review required	Yes (multidisciplinary)	Generally no, but increasing in frequency
Statistical review of data	Yes	Not normally
Regulatory burden (premarket)	High	Low to moderate
Regulatory burden (postmarket)	High	Low
Changes and modifications	Changes that affect S&E require supplement approval	Changes that could significantly affect S&E require 510(k) submission
Annual reporting requirements	Yes	No

FDA Actions	Premarket Approval (PMA)	Premarket Notification (510(k))
FDA ability to request additional information (place submission on "hold")	Yes	Yes
Panel review and recommendation	Yes (optional)	No (very unusual)
Favorable outcome	"Approval" allowing commercial distribution	"Classification" allowing commercial distribution[d]
Unfavorable outcome	Denial of approval	Not substantially equivalent (NSE) determination
Conditions of approval (COA)	Standard	NA
Postapproval studies	Frequently required as COA	NA
Control over promotion and advertising materials	Possible as COA	No
Authority to withdraw approval	Yes	No
Authority to temporarily suspend approval	Yes	No
Authority to rescind final decision	No	No
Review Times	**Premarket Approval (PMA)**	**Premarket Notification (510(k))**
FDA statutory review time	180 days	90 days
Total FDA average review time[e]	283 days	54 days
Submission Contents	**Premarket Approval (PMA)**	**Premarket Notification (510(k))**
Descriptive data	Yes	Yes
Performance data (bench and animal)	Yes	Frequently
Clinical data	Yes (original and panel track supplements)	Not usually required—FDA estimates <10% of 510(k)s
Human factors data	Increasing	Not usually
Final draft labeling	Yes	Not for compliance with Part 801
Manufacturing process details	Yes	No

continued

TABLE C-1 Continued

Submission Contents (continued)	Premarket Approval (PMA)	Premarket Notification (510(k))
Truthful and accurate statement	No	Yes
Trade name authorization	Requires FDA approval	No FDA authorization needed
Manufacturing facility inspection	Preapproval	Postclearance (biannual)
Premarket BIMO inspection	Yes	No (extremely unusual)
Contents available for future FDA decision-making	No (statutory prohibitions exist)	Yes (no prohibitions)
User Fees (2010)	**Premarket Approval (PMA)**	**Premarket Notification (510(k))**
Original application	$217,787 ($54,447)[f]	$4,007 ($2,004)
Panel track supplement	$163,340 ($40,835)	N/A
180 day supplement	$32,668 ($8,167)	N/A
Real-time supplement	$15,245 ($3,811)	N/A
30 day notice	$3,485 ($1,742)	N/A
Annual report	$7,623 ($1,906)	N/A

NOTE: BIMO = bioresearch monitoring; CFR = Code of Federal Regulations; FDA = Food and Drug Administration; FY = fiscal year; N/A = not applicable; S&E = safety and efficacy.

[a]Very few (continuously diminishing) number of 510(k) review eligible preamendment class III devices.

[b]Class I devices are generally exempt from 510(k) requirements as are other select class II devices. Other regulatory exemptions from 510(k) exist.

[c]GAO Report. Medical Devices—FDA Should Take Steps to Ensure That High-Risk Device Types are Approved through the Most Stringent Premarket Review Process. GAO 09-190. January 2009.

[d]Manufacturers of class I and II devices are prohibited by law from referring to a finding of substantial equivalence as FDA approval (21 CFR 807.

[e]FY 2006 and 2007 ODE Annual Reports. PMA times are for original and panel track supplements.

[f]Note: Small business (≤$100 million in gross receipts or sales per year) discounts provided in parentheses. Fee is also waived for first PMA submitted and approved by a business with ≤$30 million in gross receipts or sales per year.

meet users' needs. With each change, manufacturers must consider whether the magnitude of the change creates a need to obtain FDA authorization before introducing the "new" device into the marketplace. The criteria for making this decision in regard to class I and II devices are found in regulation. According to 21 CFR 807.81(a)(3), a premarket notification must be submitted when the device

> is about to be significantly changed or modified in design, components, method of manufacture, or intended use. To further clarify the regulatory standard, significant changes include
>
> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, for example, a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
>
> (ii) A major change or modification in the intended use of the device.

FDA and industry have struggled with the phrase "could significantly affect the safety or effectiveness of the device" and the use of the adjectives "major" and "significant." The subjective nature of the wording leaves room for interpretation and is a continuous source of disagreement. To address this issue, FDA issued a guidance document in January 1997 (FDA, 1997). While this guidance document has been successful, contributing to a standardized approach to decision-making, one thing has not changed: manufacturers have to assess the significance of each change to their devices and make a decision whether to file a 510(k) with FDA. The details of this aspect of US device regulation go beyond the scope of this paper, however, the regulatory issues created when regulating rapidly changing products must be a consideration when exploring alternative regulatory schemes.

510(k): Strengths, Weaknesses, and Flexibilities

Unlike most FDA premarket review programs, the 510(k) process affords the agency great discretion in how it approaches decision-making. While the law and implementing regulations provide structure to the approach, the agency always focuses its attention on the scientific and clinical issues that are of public health importance. When important issues surface, FDA has the ability to request additional information, including clinical data, when it is essential to resolving them. In the end, FDA is in control. SE determinations are not automatic and 510(k) submitters are not authorized to market their devices until FDA issues a letter specifically authorizing them to do so.

Although an analysis of 510(k) decision-making that is far beyond the

scope of this paper is required to assess the value of the program, the most recent data available from FDA demonstrate that the program is not merely a "rubber stamp" as is often suggested. For fiscal year 2007, the last year that the Office of Device Evaluation (ODE) published data on 510(k) decisions,[13] of the 3,052 decisions rendered, 2,640 (87 percent) were SE, 95 (3.0 percent) were NSE and 317 (10 percent) were "other." The basis for FDA's NSE decisions is not public, however, the bulk of NSE decisions relate to either the new device's having a "new" intended use or scientific and clinical issues relating to technology. Other decisions include 510(k) withdrawals and deletions representing manufacturers' inability, or unwillingness, to meet FDA's expectations for clearance.

Freedom to Apply Knowledge from Precedent in Decision-Making

Inherent in the 510(k) decision-making process, is the agency's ability to apply the knowledge gained from the premarket and postmarket experience with class I and II devices to the review of new devices that are the subjects of 510(k) submissions. This is in stark contrast to the PMA process, where the agency is precluded by law from applying any information obtained in one PMA submission to the next without explicit authorization from the owner of the PMA with the information.[14] This flexibility has lessened the regulatory burden associated with bringing new class I and II devices to market more than any other aspect of the 510(k) program. It has diminished the need for repetitive testing of new biomaterials to completely eliminate the need for redundant clinical studies. In the world of class III devices, every manufacturer must generate its own data on its own device and cannot rely on any data that are contained in competitors' approved PMAs.

Ability to Grant Exemptions

When 510(k) no longer provides public health value, FDA has the ability to exempt a device from premarket review. This option does not exist for PMA. The criterion for making the decision to exempt a device types from 510(k) was spelled out in the *Federal Register* (*FR*).[15] The FR notice stated:

[13]Refer to the Fiscal Year 2005 and Fiscal Year 2006 Office of Device Evaluation Annual Reports at http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm127516.pdf.

[14]Guidance for Industry and for FDA Reviewers: Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997 available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073707.htm.

[15]January 21, 1998, FR notice (63 FR 3142).

> In considering whether to exempt class II devices from premarket notification, FDA . . . (1) . . . has considered the risks associated with false or misleading claims, and the frequency, persistence, cause or seriousness of the inherent risks of the device); (2) characteristics of the device necessary for its safe and effective performance are well established; (3) changes in the device that could affect safety and effectiveness will either: (a) be readily detectable by users by visual examination or other means such as routine testing, before causing harm, for example, testing of a clinical laboratory reagent with positive and negative controls; or (b) not materially increase the risk of injury, incorrect diagnosis, or ineffective treatment; and (4) any changes to the device would not be likely to result in a change in the device's classification. FDA also considered that even when exempting devices, these devices would still be subject to the limitations on exemptions, as described in section III of this document.

The agency's position is that these same factors should also be considered when determining if any additional class II device types should be exempted from 510(k) requirements. As a safeguard, all exemptions from 510(k) are subject to "limitations on exemptions" that prohibit industry from altering the intended uses or the fundamental scientific technology upon which the exemption was based.

Determining Intended Use from Proposed Device Labeling

Section 513(i)(1)(E) of the act restricts FDA's determination of the intended use of a device that is the subject of a 510(k) to the proposed labeling in the submission. The basis for this restriction relates to FDA's historically withholding or delaying clearance of 510(k)s based on concern regarding off-label use of the device. In amending the law with FDAMA 97, Congress recognized the importance of allowing new medical devices that are SE to go to market even if a potential for off-label use is evident. Although the agency's determination of intended use is restricted, FDA is empowered to consider the potential for off-label use and act on concerns that meet specified criteria. In addressing off-label use issues, Section 513(i)(1)(E) requires FDA to consider

1. Whether there is a reasonable likelihood that the device will be used for an intended use not identified in the proposed labeling for the device, and
2. If such use could cause harm to the patient or the consumer.

In situations that meet these criteria, the agency most often mandates the inclusion of warnings, precautions or contraindications, as appropriate, in device labeling through the SE letter, often referred to as "SE with limitations." In order for recipients of these letters to modify or delete FDA

mandated labeling statements, they are required to submit a new 510(k) with scientific evidence sufficient to justify their request.

Following enactment of the statutory provision in 1997, critics of this statutory provision initially envisioned industry taking advantage of this "regulatory loophole" by labeling their devices one way to get clearance while really intending their devices for uses that do not appear in labeling. Manufacturers of biliary stents, a class II device, have engaged in activities that appear to support this concern. Many manufacturers of biliary stents have engaged in promotional activities geared toward the needs of cardiac surgeons and their patients. These practices suggest that obtaining FDA clearance for biliary use was a ruse to avoid the rigors of PMA approval for class III stents intended for use in the vasculature. Regardless of the manufacturers' intent, the challenge relating to this situation affects the PMA path to market as well as 510(k). Devices in all regulatory classes that are labeled with legitimate indications for use can be, and often are, used for off-label uses. To completely avoid this situation, FDA would have to either prohibit distribution of the devices for the legitimate on-label uses or somehow interfere with the practice of medicine—two options that are subject to legal challenge and are not good for public health.

While the merits of the way FDA handled the biliary stent situation can be debated, the biliary stent situation serves as evidence that there are post-market means of addressing an issue after FDA grants market authorization, as the FDA took the manufacturers to task via a systematic compliance action that effectively stopped the rampant off-label promotion and use of biliary stents for cardiac indications.

Least Burdensome Provisions of the Law

With enactment of FDAMA 97, Congress wanted to reduce unnecessary regulatory burdens associated with the 510(k) and PMA processes. Although the Congress did not change the statutory criteria for FDA decision-making, it sent a clear directive to the agency to eliminate any unnecessary burdens that contribute to delay in the availability of new medical devices. To this end and in regard to the 510(k) program, Section 513(i)(1)(D) of the act states:

> Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such a request, the Secretary shall consider the *least burdensome* [emphasis added] means of demonstrating substantial equivalence and request information accordingly.

In regard to PMA requirements, Section 513(a)(3)(D)(ii) states that

> any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

To implement these statutory provisions, the agency issued a guidance document for FDA staff and regulated industry (FDA, 2002). In defining the term *least burdensome*, the agency took great care to fulfill the intent of Congress while maintaining the integrity of the review processes. In this regard the term was defined as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA." In reality and recognition of the common sense nature of the provision, FDA applied the least burdensome concept to all devices regulated by FDA under the device provisions (including IVDs). In so doing, FDA believed that the statutory mandate could be accomplished without compromising scientific integrity in the decision-making process or FDA's ability to protect the public health.

Just as the words *substantial equivalence* often create visions of an inferior or out-of-date regulatory threshold for clearance, the words *least burdensome* create visions of scientific shortcuts or compromise. In considering the least-burdensome provisions and need for regulatory reform, it is important to avoid perception and focus on fact. In this regard, we are fortunate to have detailed guidance that clearly articulates the agency's intent in implementing the least-burdensome provisions of the law. When the guidance is carefully read, it is clear that only shortcuts and compromise that do not lower FDA's standards fall within the meaning of the terminology.

Accommodating New Scientific Knowledge in the Review Process

Science is constantly evolving, creating new methods for conducting research, exploring what was thought to be known to a much greater depth than thought imaginable, and identifying new issues that warrant investigation. In a regulatory setting, this creates a significant challenge. On one hand, regulated industry appreciates new scientific methods that result in efficiencies and cost savings. On the other hand, industry resents having new products withheld from the marketplace pending the conduct of testing that the competition may not have conducted. While this issue is present across the board, including the PMA process, there is no simple way of addressing this dilemma within the system of device regulation embodied in 510(k).

Interestingly enough, the challenge is less pronounced in regulating new devices with differing indications for use or technological characteristics. Under these circumstances, industry takes little issue with performing state of the art tests on the way to market entry. Ironically, the challenges most often surface with "me too" devices that are held to a higher standard than their predecessors because of new scientific information about the products or the materials, or new methods of assessing products.

Take electromagnetic compatibility (EMC) as an example. Not too long ago, little attention was paid to electromagnetic emissions, giving way to devices that either interfere with other devices being used in close proximity or are themselves susceptible to interference. When electromagnetic interference became a recognized environmental hazard the regulatory process was not prepared to respond. The initial response was to hold new devices entering the marketplace to a higher standard that included difficult to conduct EMC testing. This mindset delayed new products getting to market and prolonged the use of older designs.

What is needed is a means of encouraging the development of improved technology that is not dependent on premarket review to implement. The development of performance standards or agency guidance that encourages product improvement over time with verification of company progress during FDA facility inspections is a viable model. Here the use of international standards would have some applicability as well, though ensuring those standards are kept up to date remains a significant challenge outside FDA purview. The development and issuance of guidance by FDA as new knowledge accrues would be a powerful tool and if communicated effectively to industry would promote innovation and also speed product to market while addressing new scientific concerns.

Illustration 5 Computer assisted diagnostic (CAD) devices.

Computer assisted diagnostic devices are a relatively new phenomenon. And as they have developed, FDA has been in the forefront of developing methods to evaluate these products. The research and attendant methods have changed significantly over the past decade and thus the questions that reviewers may be asking today about product performance parameters are dramatically different than what were asked previously. For example, in the early 1990s the focus was on sensitivity and specificity. Today, FDA has shifted to evaluating area under the receiver operator curve (ROC) and to assessing multiple case–multiple reviewer study paradigms. Initially, not all of the appropriate questions relating to CAD were addressed in determining device safety and effectiveness. This means the evaluation methodology for CAD products has changed because of advances in understanding and science.

We note that if new scientific knowledge suggests that devices on the market are not safe, then 510(k) is not the appropriate regulatory mechanism to address the issue. If the new scientific information raises issues that would question prior decision-making, then FDA should resolve them without disadvantaging select companies and through maintaining a "level playing field." If FDA has concerns with a group of devices, the agency has the means to rectify the situation without disadvantaging companies seeking market authorization for new devices. Promulgation of special controls, including mandatory performance standards, issuance of public health advisories, guidance documents and agency use of the "bully pulpit," is an effective means of prompting change. If FDA has information that suggests that a product is not safe, a range of compliance actions can be selected from the menu, including issuance of untitled letters and warning letters, requiring mandatory recall, charging civil money penalties for every violation, as well as seizure and injunction.

Ultimately, this is a challenge for FDA. Consideration must be given to establishing streamlined mechanisms for addressing issues recognized through new scientific means. The American public would be better served if FDA had more efficient and effective means of requiring companies to take corrective action. The promotion of voluntary consensus standards presents an unrealized opportunity for FDA reviewers to address scientific issues that the concept of substantial equivalence to marketed products does not.

The Unrealized Potential of National and International Standards in Review

As of June 2010, CDRH recognizes 833 national and international device standards. These are largely of two types. Horizontal standards are broad and cover issues that affect many types of devices. Examples include the standards for safety of electrical products (IEC-60601-3) and risk management for medical devices (ISO 14971). The third edition of IEC 60601 is an all-hazards standard for devices that use electricity and the standard is generally about the safety of these products. ISO 14971 is a relatively new standard and sets out principles for how to manage risk at all points across the medical device product life cycle. The other type is vertical standards which are less general and are very product-type specific.

Failure to conform to a recognized standard after submitting a declaration of conformity in a 510(k) or PMA is a prohibited act, subject to FDA enforcement action.[16] By declaring conformance to a recognized standard, a company can avoid submitting detailed documentation regarding the issues

[16]Refer to Sections 301(x) and 501(e)(2) of the act. Submitting a false declaration in a premarket submission is a violation of the law.

covered by that standard. In fact, Section 514(c) of the act directs FDA to recognize national and international standards, and mandates that FDA will accept a manufacturer's declaration of conformity to an FDA-recognized standard to meet a requirement to which the standard is applicable. It also requires the manufacturer to maintain information demonstrating conformity. The manufacturer must have this information at the time a declaration is submitted and must provide the information to FDA upon request.

By virtue of the rules of standards development organizations which generate the standards that FDA recognizes, it is clear that credible standards do exist. However, the standards process is also burdensome and a theme with respect to standards, much like guidance, is that by the time a document is issued, the science may have changed making parts of these documents out of date. This heightens the need for the review teams in FDA to maintain a high level of current knowledge about science and standards and to maintain some degree of review flexibility. More importantly, the FDA needs greater involvement in assisting in updating international standards.

Are criteria for applying these standards transparent and grounded in good science and do they lead to good health care? All medical device standards are developed to help ensure safety and effectiveness leading to good public health. Many standards provide this information and others are improving. For example, if one follows AAMI/ANSI/ISO 10993-1:2009, a horizontal biocompatibility standard, the standard defines the principles and criteria for effective use of the standard with a flow chart summarizing the systematic approach to a biological evaluation of medical device materials as part of a risk management process.

The rate limiting factor in the use of standards has been manufacturers' unwillingness to submit declarations of conformity in premarket submissions. This unwillingness is fueled by three risks: (1) the threat of immediate inspection, (2) the likelihood that a disagreement with FDA will ensue regarding conformity with a standard, and (3) the possibility of criminal prosecution should FDA conclude that conformity with the standard did not exist at the time that the declaration of conformity was submitted for FDA review. Fears of these risks persist and have resulted in low standards use.

For consensus standards to optimally contribute to public health, industry needs to support the establishment of more robust standards, including standards with "performance limits," and to be willing to declare conformity in all premarket submissions. Taking this approach can encourage innovation and afford regulators the confidence that testing against the standard ensures that the device performs as intended and designed. Furthermore, FDA needs to expand the concept of conforming to standards to include conformance to FDA guidance as a viable and highly desirable approach to securing FDA market authorization.

CHALLENGES CREATED BY INDUSTRY, COST CONTAINMENT, AND THE PRACTICE OF MEDICINE

Industry Competition Prompts Device Differentiation

The medical device industry is a very competitive industry. While technology has evolved at a tremendous rate ever since passage of the MDA 76, technology is only one part of the competitive equation that challenges device regulation. In fact, in some respects technology is the easiest variable to deal with in the confines of 510(k) review. New technology either is found to fall within an existing generic device type or raises significant enough public health issues to warrant premarket approval.

Perhaps the most challenging aspect of competition in the industry relates to device labeling and promotion and advertising practices. As has been pointed out, in order for FDA to authorize a manufacturer to market a new device through the 510(k) process, the agency must conclude that the new device is SE to an existing class I or II device. While being SE is a prerequisite to obtaining FDA clearance, new devices can and do differ from the devices to which they are compared. In the highly competitive medical device industry, manufacturers attempt to differentiate their devices from the competition, but not to a degree where FDA finds them to be NSE. For devices that are similar in design and function to competitors' devices, the most common way to achieve differentiation is through descriptive information (for example, "claims") added to product labeling, or disseminated through promotion and advertising materials and activities. It is not unusual for manufacturers to attempt to use the 510(k) process to get FDA authorization to add descriptive information to device labeling. In an FDA guidance document, the agency acknowledges this industry approach to differentiating devices in order to capture market share from competitors.[17]

Drivers of Change: Cost Containment and the Practice of Medicine

The quest to control spiraling health-care costs is a major factor that influences device design and use today. When combined with the ever changing demands imposed by the practice of medicine, significant forces are created that drive the medical device industry to innovate. The result stresses the FDA bureaucracy and slows progress. One need only consider the impact of medical errors on the evolution of medical technology. Everyone knows that the costs associated with medical errors are high, leading to escalating health-care costs and awards associated with expensive litigation. Pressure from the health-care community and insurance providers, along with prac-

[17]Refer to Guidance for Industry: General/Specific Intended Use at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm073944.htm.

titioners, to reduce medical errors incentivized the development of software controlled devices, networked systems and interdevice compatibility. More sophisticated device–user interfaces are associated with the resulting technology fueled human factors considerations, all of which have created sudden and significant challenges for FDA's premarket review programs.

Consider the evolution of single use devices (SUDs) and the reprocessing industry that was spawned to allow the reuse of SUDs as a means of cost containment. SUDs were initially developed to reduce the risks associated with hospital and doctor office cleaning and sterilization procedures and to eliminate the costs associated with these procedures. Escalating health-care costs soon after created opportunities for third party reprocessors to engage in activities designed to render SUDs suitable for unanticipated reuse. These dramatic shifts created major challenges for FDA that were only overcome through legislative change.

Combination Products

A scientific and regulatory complexity that has surfaced in the last 20 years with increasing frequency relates to combining drugs and biologics with medical technology. Whether simple antimicrobial coatings added to devices to increase resistance to infection, complex drug coated cardiovascular stents to prevent restenosis, or sophisticated drug and biologic delivery systems, an explosion of regulated entities that cross traditional FDA regulated product boundaries has created immense challenges for FDA. From a regulatory perspective, a device that contains, or is otherwise associated with, a drug or biologic agent may be a "combination product." Combination products present complex regulatory issues, including what FDA requirements apply to the combination product and which FDA center has responsibility for ensuring that the appropriate requirements are met. For combination products assigned to CDRH, the complexities go deeper when considering the proper device classification. For class III devices, regulation can be reasonably straightforward, but for simple devices, the addition of drugs and biologics can create complex scientific issues.

FDA's Office of Combination Products (OCP) determines which FDA regulated products meet the definition of a combination product, as well as which center assumes the responsibility for the combination product's regulation. For combination products, typically one FDA center will have responsibility for the product's regulation, but all centers with expertise relevant to the product play a role in the product's evaluation. While a treatment of how this will play out with respect to various device regulatory approaches is beyond the scope of this paper, it seemed worthy of a mention within the broader context of considering whether the statutes that govern FDA's device program provide adequate protection of public health.

A PERSPECTIVE ON FDA GUIDANCE DEVELOPMENT

FDA guidance documents have been demonstrated to be a valuable way of articulating agency expectations while establishing a reasonable degree of consistency and predictability in the review processes. We hasten to add two points concerning agency guidance. First, in practice some members of both FDA and industry have interpreted guidance as de facto regulation. For guidance to be of maximum value, guidance *must* be treated as exactly that: "guidance"—information intended to help industry and FDA in achieving consistency in review and predictability in outcome. It should not be used as a straitjacket that hampers innovation or delays getting products to market. Guidance should facilitate development and, when used appropriately, lead to a streamlined means of developing data for regulatory submissions and improved submission quality, a source of significant delay in the regulatory process. The second point relates to the procedural issues in developing guidance in FDA. Guidance development has become as difficult as issuing a regulation. The current approach to development of guidance is needlessly burdensome on all parties and displays the bureaucracy failing in a simple, but effective means to promote and protect the public health.

CONCLUSION

Ensuring that all medical devices are safe and effective entails a complex system of requirements, with Section 510(k) being one component. A fair assessment of the US regulatory system requires careful consideration of each system component and the relationships between components that provide the system's overall functionality.

The 510(k) process differs from how it is often characterized. In fact, the most common characterizations of the rather complex concept of SE are as simple as the acronym and are often misleading. While the 510(k) program has strengths and weaknesses, without question the program makes significant contributions to public health. Whether the program is maintained "as is," changed or totally abandoned, the US regulatory system for ensuring the safety and effectiveness of the diverse range of medical products that fall within the definition of *device* must be flexible enough to accommodate constant and rapid change, and have the integrity to fend off criticism. For FDA scientists and clinicians, making correct decisions is difficult enough without having the underlying regulatory process for those decisions under constant attack.

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Appendix D

Impact of the Regulatory Framework on Medical Device Development and Innovation

David W. Feigal, Jr., MD, MPH

The pace of innovation for regulated products is the combination of the speed of the development of science and engineering needed to make science-based regulatory decisions. Just as innovative medical products have a life cycle, from concept to obsolescence, new scientific and public health challenges have a life cycle. The two are intertwined and the lack of speed in scientific developments and the lack of a responsive science-based regulatory decision-making process can both slow progress. The US Food and Drug Administration (FDA) Critical Path initiative focused on the science of development: better toxicology, biomarkers, improved clinical trials, and personalized medicine, but that initiative, like others including the re-engineering initiatives of the 1990s and legislative changes that accompanied device user fees, did not examine the regulatory structure of the approval process itself and how the regulatory structure determines the choices in the science of development.

SCIENTIFIC AND PRODUCT LIFE CYCLES

In 2003, severe acute respiratory syndrome (SARS), a coronavirus causing severe sometimes fatal pulmonary infections, emerged in China and rapidly spread around the world (Anderson et al., 2004). Pandemics have a life cycle characterized by rapid worldwide spread which grows as long as each new infected person on average transmits the infection to more than one other person. An effective public health response in the life cycle of a new potential pandemic threat begins with identification of cases (see Figure D-1). Sometimes the first case in a community can be identified,

FIGURE D-1 The life cycle of the public health response to a new infection.

but more often the threat is recognized as clusters and then communities develop disease.

Collections of body fluids or tissue specimens are needed to identify the pathogen. Diagnostic devices are often an important element in an effective public health response to break the cycle of spread and prevent the emergence of new cases. The World Health Organization estimated that there were 8,096 cases with 774 deaths in 2002 and 2003 (Anderson et al., 2004; WHO, 2004). But by 2006 this SARS pandemic threat had been completely contained.

Parallel to the scientific and public health life cycle is the in vitro diagnostic product life cycle (see Figure D-2). As the clinical specimens from infected patients become available, the search for a pathogen begins. As infectious candidates are identified, analytes, the active ingredients of in vitro diagnostics, are created to develop investigational diagnostic devices. In 2003 SARS-infected clinical specimens were scarce, but with the pathogen identified "spiked" samples could be developed to refine diagnostic methods. Investigational diagnostics for emerging infections are initially tested against available specimens from sporadic cases and epidemiologic studies. As the test develops it may be prospectively studied to evaluate new cases and make decisions about clinical treatment or quarantine. Patient research

protocols and informed consent are often required at this time. As the test matures the quality system manufacturing processes prepare for commercial scale production. Once introduced into the market and in widespread use it isn't long before the development life cycle repeats as the next generation tests are developed and improve the diagnostic test.

The scientific and product life cycles are interconnected and involve coordinated efforts by clinicians, academic research groups from many scientific disciplines, local, national and international public health organizations, and the regulatory oversight of research by institutional review boards (IRBs), clinical laboratory licensing agencies, such as the Clinical Laboratory Improvement Amendments (CLIA) program in the United States, and last but not least, the regulatory oversight of investigators and the device manufacturers by the FDA and other national device regulatory authorities.

While the effectiveness of the public health measures to control SARS forestalled the need to develop a commercial widely available diagnostic, the tools for innovation provided by molecular methods allowed public health laboratories and multiple in vitro diagnostic (IVD) manufacturers to have the investigational diagnostics available to help in the public health response. Another example of rapid development, approval and use of a new diagnostic, still in use, is the blood screening test for West Nile disease available since 2003.

FIGURE D-2 The scientific life cycle of a new in vitro diagnostic device in vitro diagnostic device.

THE TOTAL PRODUCT LIFE CYCLE AND FDA'S DEVICE REGULATION

For the last decade the Center for Devices and Radiological Health (CDRH) at FDA has promoted the total product life cycle as a framework for medical device regulation. The origins of the US medical device laws were embedded in the US drug laws, and before the 1976 Device Amendments to the Food, Drug, and Cosmetic Act, some medical devices were approved with new drug applications (NDAs).[1] As it began, device regulation largely reflected drug regulation. The initial medical device good manufacturing practices (GMPs) borrowed heavily from drug GMPs, the investigational device exemptions (IDEs) were patterned on the investigational new drug exemptions (INDs), and the premarket authorization (PMA) process borrowed advisory committees, preapproval inspections and clinical trial evidence standards from the NDA process. Drug regulation's most powerful tool—the authority to approve drug marketing—became a key milestone in device development. Much of drug regulation is framed in terms of premarket and postmarket requirements. But device regulation does not fit as well into this simple premarket–postmarket regulatory framework.

While digoxin has always been and always will be digoxin and penicillin always will be penicillin, medical devices which are not as much discovered as they are designed, are iteratively developed technology. Devices have physical properties and performance characteristics that can be tailored for use, directly observed, and modified. Designs evolve throughout early development from prototype to bench testing to the clinical experience and use in IDEs and even once in the marketplace. Individual device failures provide opportunities for iterative improvements. The more complex the design, the more likely the product will rapidly evolve. All the phases of the device life cycle are interconnected and include connections across generations of a device.

Device consumer protections since the device amendments have recognized that wide range of potential device hazards and that the extent of regulation should be proportional to the level of risk. One of FDA's first tasks in the 1970s was to classify devices and determine risk levels. While the basic regulatory framework put in place in the 1970s remain, the requirements began to evolve away from the drug regulatory paradigms. In the middle 1990s the device quality-system manufacturing requirements replaced the more drug-like GMPs. In 2000 CDRH began to create programs that combined the regulatory programs across the product life cycle and were tailored to the specific risks and clinical uses of particular products. The Division of In Vitro Diagnostics within the Office of New Devices became

[1]Products approved before 1976 with NDAs are referred to as transitional devices in 520(l) of the FDCA.

the first TPLC (total product life cycle) program combining together all the regulatory teams with IVD responsibilities from premarket and postmarket surveillance to compliance activities.

Without accounting for iterative innovation it is difficult to design long term postmarket studies for a product which will be replaced in a year by the next generation of that manufacturer's product. The best source of safety information about a product not yet cleared or approved for marketing may not be the preclinical testing of the new product, but the postmarket experiences from previous generations of the same product. Judicious device design changes during investigational or marketed use encourages innovation and optimization, and CDRH provided guidance on how much a product can be changed before it is a new product (FDA, 1997). A product designer or regulatory reviewer will have more insight into design challenges when considered along with failure mode analyses done after the recall of a similar product or in light of the product specific problems identified on compliance inspections. The science is all interconnected across the life cycle, not just for the innovative product developers, but also within the FDA and other regulatory bodies.

An interconnected life-cycle vision of medical device innovation emphasizes the need to link the diverse scientific disciplines and the regulatory mechanisms (see Figure D-3). Early in the process the device engineers develop prototypes and begin bench testing different designs to evaluate biocompatibility, or strength or flexibility, for example. FDA provides guidance to determine if the product will be regulated as a device, and if so, at which risk classification and product group. Specific guidances have been developed for many products on specific standards and regulatory requirements. Primary mode of action and intended use both guide the design and shape the regulatory path.

When products require clinical testing both the manufacturer and FDA will involve clinical scientists and statisticians and IRBs. Regulatory meetings may produce agreements and provide advice on the scientific evidence needed for regulatory decisions leading to market clearance or approval. Formal advisory panels may become part of the process for external scientific advice and CDRH calls on panel members for advice between meetings. Later in the life cycle the scientific disciplines become less experimental and more observational as medical device reporting (MDR) provides signals of potential new problems. Failed devices are analyzed and compliance inspections ensure appropriate quality systems. Some products need to be recalled, others grow old gracefully and are replaced by newer products over time. Devices frequently are improved by considering human factors engineering, training, and the diversity of clinical use. As illustrated in Figure D-3, both the scientific and regulatory processes are intertwined throughout the product life cycle. Just as different parts of the science life cycle are intercon-

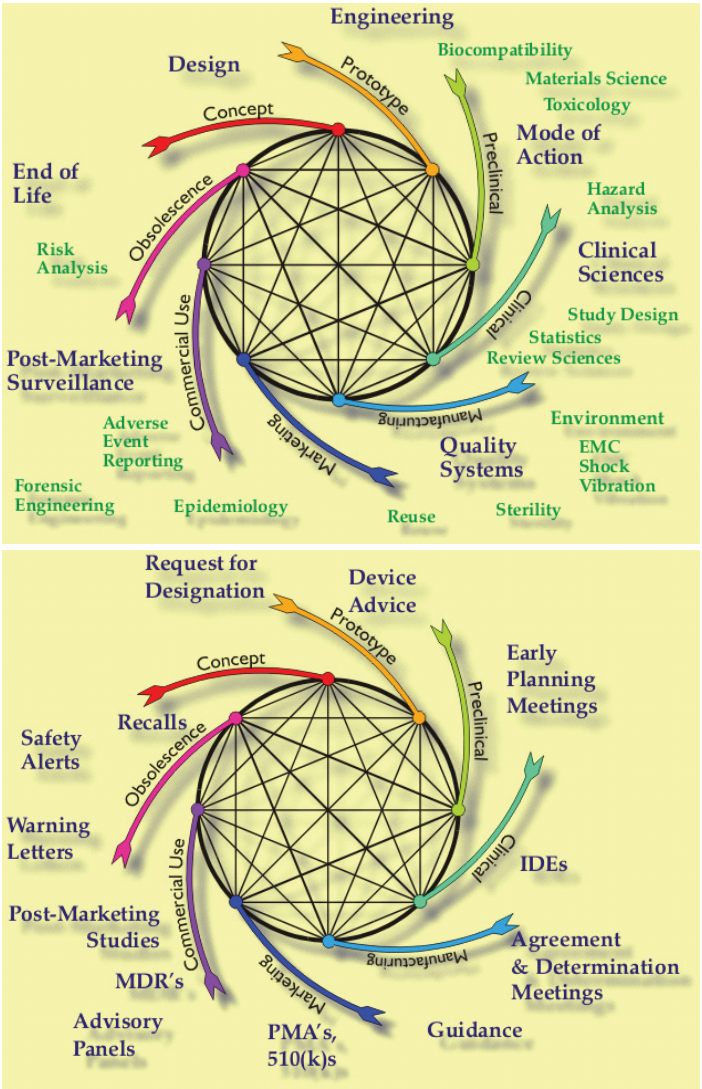

FIGURE D-3 Total product life cycle. The science cycle and the regulatory cycle.

nected, the science and the regulatory requirements are intertwined, each informing and determining the other. There is an opportunity to build the connections, both at FDA and in manufacturers, so parts of the life cycle do not risk only being considered in isolation. For example, it is not uncommon for a premarket application to be reviewed without considering postmarket experience of similar products.

RISK CLASSIFICATION AND INNOVATION

Medical device regulations, around the world, begin by assessing the risk of the device and more specifically, the risk of the intended use of the device. The regulatory requirements (or "burdens," as the US Congress implies when the statute refers to the "least burdensome regulatory path") are proportional to risk. The lowest risk devices are required to meet general controls, register their facilities and list their devices but in large part are only regulated by FDA "for cause" when problems are identified. The highest risk products, the class III PMA products have development paths that are very similar to new drug development, as described briefly above. There have been as few as a dozen and never more than a hundred new PMAs in a year although there are also several hundred supplements and IDE protocols to review. The class III products occupy a disproportionate share of the review and inspectional resources at FDA. The ten to twenty new PMAs and the several hundred supplements, by CDRH's estimates, occupy as much review time as the 3,500 501(k) applications. While PMAs require a preapproval inspection, 510(k) inspections are worked into the schedule of routine inspections, and the PMA products are far more likely to be topics at advisory panel meetings. The flexibility of the supplemental PMA process, the process to modify an approved PMA product, includes regulatory innovations such as real-time review and accelerates the innovation life cycle for these products, once initially approved.

CDRH summarizes the number of applications received and the review performance every year in an annual report that can be found on the FDA Web site (FDA, 2008). The approximately 3,500 class II 510(k) notifications each year represent the bulk of new devices with active FDA oversight. To achieve a steady state CDRH must clear approximately 15 notifications each business day. The review time to final action is accomplished more than half the time within the 90 day review clock. Historically CDRH has estimated that about 25 percent of its staff devotes their time to 510(k) activities which is not more than 20 days review time per application. By contrast the review of NDAs, biologic license applications, and even PMAs is measured in person-years not person-days. 510(k) notifications, however, do not have supplements or annual reports and these estimates do not count the regulatory hours spent on the rest of the product life cycle such as postmarketing

surveillance and compliance activities. Even if all of CDRH's resources were dedicated to class II products, at current staffing, there would be no more than 0.25 person-year per application for review. Class II review cannot be modeled on NDA or PMA review, and because requirements should be proportionate to risk, the design of the class II regulations must be streamlined, as they are now, compared to PMA reviews.

The large difference in regulatory burden between class II and class III applications allows the development of smaller companies and more rapid product innovation cycles. While small companies have completed PMAs, the majority of class III products are developed by the larger medical device companies. The two factors that have the biggest impact on regulated product development are review cycle time and level of evidence requirements. The impact of the short review cycle can be illustrated when comparing US PMA products to European class III products. Because the US review cycle for some products is twice as long as the European cycle, not only are innovative products introduced later to the US markets, but the US markets miss every other new model when the PMA supplement review cycle is twice as long as the innovation and approval cycle outside the United States.

Risk reclassification is a difficult process for CDRH. Innovation is hampered when a product is classified in too high a risk class. The infrequency of reclassifications and the ponderousness of rule making which can add years of delay to implement reclassification decisions combine to slow the pace of implementing scientific change. The statutory default which assumes novel products, that is, products without a predicate, are class III products hampers innovation.

DEVICE CLASSIFICATION AND INNOVATION

By page volume, the largest part of the US FDA device regulations are devoted to describing approximately one thousand different medical device classifications. Along with risk classification, device classification is a strong determinant of the regulatory requirements for specific products. Each device classification has its own section in the regulations, and approximately half of all products approved also have an FDA guidance document that provides FDA's best advice on regulatory requirements necessary for clearance or approval. The products with guidances have both a more rapid review cycle and a higher probability of first cycle approval. Products with guidances were also the first products that FDA allowed to be reviewed by third-party reviewers. Guidances advise not only the innovators but also FDA review scientists, which may account for the predictably faster review cycles.

LEVEL OF EVIDENCE AND INNOVATION

Finally, once risk classified and product classified that last determinant of the regulatory requirements is the product's intended use. 510(k) clearance requires demonstrating substantial equivalence to one or more predicate devices with the same intended use. It is often the case that the predicate will be an earlier version of the same device from the same manufacturer, but a predicate can be any medical device marketed before 1976 or legally marketed 510(k) since. FDA has weak authorities to remove obsolete products and critics of the 510(k) process worry that comparison to any available predicate is a low bar. While guidances and standards can recommend more stringent requirements FDA cannot require them.

The extent and type of evidence are determined by the intended use. The same product can have more than one intended use. Different intended uses can even result in different risk classifications. To illustrate, a diagnostic device for cancer prognosis in someone already known to have breast cancer is a class II risk device. The same diagnostic, if *solely* relied on to make a specific treatment decision for breast cancer, would be a class III risk device. The level of evidence for prognosis could be based on retrospective observational data while the evidence for a treatment decision would likely require a prospective clinical trial.

"Tool claims" have less burdensome evidence requirements than specific clinical benefit claims. CT scanners are class II products. The quality of the images is assessed in light of the risks of the radiation exposure. Producing images is a "tool claim." NIH is conducting a large trial to assess whether CT scan detected pulmonary abnormalities results in clinical benefit from earlier detection of lung cancer. If established, FDA could allow "detection and prevention of morbidity from lung cancer" as a claim or intended use. Not having explicitly established a clinical benefit from CT images has not kept the products from the market. Innovation in image quality and speed of image acquisition would likely not have occurred if product innovations required demonstration of clinical benefit.

Innovation is often established in research and practice outside of the regulatory framework. Laparoscopic cholecystectomy was first conducted in 1987 using laparoscopic tools developed for gynecologic surgery (preamendment devices). Adoption by general surgeons was rapid and by 1992 an NIH consensus conference recommended it as the treatment of choice (NIH, 1993). Randomized clinical trials were never done. "Tool claims" are often controversial, particularly for surgical materials such as patches or artificial membranes, as illustrated by public discussions of the concerns around surgical materials for meniscus repair, or surgical mesh for pelvic surgery.

STANDARDS AND INNOVATION

Embedded in the evidence requirements for approval and clearance are many standards. There are thousands of useful standards documents including biocompatibility testing standards, physical characteristics of biomaterials, metallurgy standards for implants or surgical equipment, electromagnetic shielding requirements, aseptic and sterile manufacturing standards to name a few. CDRH has recognized the use of approximately 500 standards. One special set of standards are the harmonization documents of the Global Harmonization Task Force, with the goal of harmonizing regulatory bodies. CDRH scientists participate in committees of the standards organizations and have a formal recognition process for standards which can be used in the 510(k) process. Just as FDA guidances promote innovation, standards provide a predictable regulatory framework. Predictability promotes innovation.

CLASS II PRODUCTS "WITH CLINICAL" AND INNOVATION

Many countries have four risk levels, most by splitting the class II products into those which require clinical testing as part of their special controls vs those which can be evaluated at the bench. Approximately ten percent of US 510(k) notifications rely on clinical testing as part of the evidence for substantial equivalence to a predicate device. Sometimes the clinical experience is integral to evaluating the performance standards required to assess the device and other times the clinical experience is required to develop training materials or to do human factors studies to ensure safe use.

Class II implants are a sometimes controversial example of these products. Since 510(k) applications have no annual reports or supplements the manufacturer decides whether changes in the product require a new 510(k). An implant with a specific design that had been clinically tested could be changed and introduced to the market without additional testing if the manufacturer concluded the change was allowed without a new 510(k). The product on the market would not match the product in FDA's records. Unintended consequences of the changes may be difficult to detect. By not having a FDA review, the opportunity is lost for FDA to detect a problem, unknown to the applicant, that had been seen in a similar product from a different applicant. The 510(k) process can be criticized for creating opportunities to not conduct trials.

EXCLUSIVITY, TRANSPARENCY, AND INNOVATION

FDA approved pharmaceutical and biologics products can obtain exclusivity when they are new molecular entities, obtain new indications with

clinical trials, are orphan products,[2] or have been the subject of certain pediatric studies. The progress made in orphan drugs and the development of pediatric pharmaceutical products after exclusivity was provided in new laws are examples cited of the role that incentives play in innovation.

There are no provisions for medical device exclusivity, even for the humanitarian device exemption products. It is not that the medical device innovators do not benefit from patents and intellectual property protections. The nature of medical devices themselves, often complex products with multiple components and rapid market cycles, makes exclusivity more difficult to define. Other than a rule which specifies a time limit during which FDA cannot rely on evidence from other applications, exclusivity is not a feature of device regulation.

More important to innovation is the transparency of the FDA processes. FDA is unique in the breadth and scope of its medical device regulatory decisions. In Europe, the early development process is divided between approximately 50 third-party notified bodies which have the sole delegated authority for premarket review in the European Union. Their review information is not shared. European postmarket surveillance is divided between the member states. No other regulatory body has as many medical device applications, public meetings, or guidances or has the small business assistance programs of FDA's CDRH. Innovation is greatly fostered by this transparency.

BIOMATERIALS, COMPONENTS, PARTS, AND INNOVATION

The regulatory framework for innovation is more uncertain for components or accessories that are not approved in their own right. The components are not without oversight. If the biomaterial is part of an implant, standards such as the ISO biocompatibility testing standard specify safety assessment requirements. If the material is on the surface of the implant there are testing standards for wear and durability. If it changes the clinical risk to benefit ratio, for example by preventing lead fracture or infection, scientific evidence would be required if the manufacturer would like to base a new claim on that innovation.

There are many components that are difficult to individually assess in any scientific testing process. In a complex device this may be true of most of the parts of the device. But the answer is not to try and solve this in the development and design phase and the 510(k) clearance review alone. The quality of the device needs attention throughout the product life cycle. Innovations in medical devices are not just big fixes and big improvements.

[2]A drug or biologic orphan eligible for 7 years of marketing exclusivity is a product where the indication for use will not exceed 200,000 individuals.

Devices are products that can be continually improved. The regulatory framework becomes a problem when it creates disincentives to improve and innovate. An option to modify and change class II products would need to be less burdensome than the PMA supplement process, but it could create a clear path to innovation.

CLASS II LABELING AND INNOVATION

At first look, it would appear that the 510(k) process discourages innovative use since clearance is based on showing substantial equivalence to a predicate device in order to make the same labeling claims. If the claims are changed, a new 510(k) is required to make the same claims as some other predicate. For example, a replacement knee joint that is glued in place and the same prosthesis intended for use without glue require a different 510(k). There are separate device classifications for the two intended uses. How then is the 510(k) process able to foster innovation? Arguably with adjectives and adverbs and a flexible interpretation of the word *predicate* by FDA. Substantial equivalence is not the device counterpart to generic drug bioequivalence. In the latter the products are expected to be interchangeably alike, but the devices have to be "as good as" or better. A rapid pregnancy test can be substantially equivalent to a slow pregnancy test but a rapidly absorbed generic would not be bioequivalent to a slowly absorbed reference product. The effect of 510(k) labeling constrains innovation to the framework of the predicates' labels.

HUMAN FACTORS AND INNOVATION

Medical devices usually require an operator, sometimes with considerable training and skill. One important component of labeling for many products is the IFU, the instructions for use. User errors are a common safety problem for medical devices, even when the device is not defective and is functioning as intended. Training programs and human factors engineering not only improve safe use but contribute useful information throughout the product life cycle to improve the design to minimize errors. Designing medical gas delivery devices so that a vacuum hose can't be hooked up where the oxygen hose was supposed to be is a simple example of human engineering.[3] A product with technology that has human factors innovations is particularly important for high risk devices and medical products designed for home use.

[3]Which has not entirely prevented users from welding a custom adapter to thwart that protection, an example of reverse human engineering.

"LEAST BURDENSOME" AND INNOVATION

The 2007 FDA Modernization Act (FDAMA) required CDRH to use the "least burdensome path to market" for medical devices. The legislation deregulating dietary supplements (the Dietary Supplement Health and Education Act of 1994) provides ample evidence that claim creativity, for better or worse, is greatly enhanced by reduction of regulatory oversight. More examples of the impact of regulation and innovation are found in the gaps between FDA and other consumer protection regulations.

Laboratory developed tests[4] fall in such a gap between FDA's regulation of in vitro diagnostic devices manufactures, the CLIA regulation of clinical laboratories, and the state medical boards' regulation of the practice of laboratory medicine. The widespread use of FDA cleared general purpose laboratory equipment, such as the polymerase chain reaction, to detect specific nucleic acid sequences has allowed laboratories to offer hundreds of different genetic tests, few of which have been evaluated by FDA.

CLIA has standards for the quality of laboratory processes but does not evaluate individual tests. Many of these diagnostics are used to evaluate reproductive risks for genetic disease or diagnose genetic diseases. FDA would clearly classify many of these devices as class III or class II products and require PMAs or 510(k)s if applications were submitted. Of these genetic tests, only about a dozen have been approved by FDA. Aside from the interesting legal questions about FDA jurisdiction,[5] the fact remains that IVD manufacturers have not brought forward innovative genetic diagnostic tests through either the 510(k) or PMA processes. Some argue that these small markets do not support the cost of the regulatory requirements to get to the market. On the other hand, the state of New York requires review and approval by its own state health department reviewers, and requires payment of a user fee and many of the lab-based tests (LBTs) meet those regulatory requirements. Perhaps the low regulatory hurdle at the front end of the product development life cycle promotes innovation.[6] Several public advisory committees, such as the Secretary's Advisory Committee on Genetics, Health, and Society, have expressed concerns about the lack of FDA oversight. Innovation with biomarkers is even more complicated since the Center for Drug Evaluation and Research has expressed a strong preference for only approving indications that are guided by a diagnostic when the diagnostic is FDA approved.

[4]Also called home brew diagnostics.

[5]FDA asserts it has jurisdiction but lacks resources and has targeted tests advertised directly to consumers and cancer related tests.

[6]Nuclear medicine physicians also have a non-FDA pathway for early development of nuclear medicine diagnostic imaging reagents. The PET scanner developed a large body of clinical evidence in multiple diseases before ever being evaluated and approved by FDA.

RECOMMENDATIONS TO PROMOTE INNOVATION IN CLASS II PRODUCTS

With innovation in mind, what changes could be made to improve innovation for class II products?

Remove the requirement that novel products are class III (PMA) products by default. Although the de novo process is a work around, the assumption that novel innovations are synonymous with high risk is not correct.

Create a class II approval process. The 510(k) procedure deserves its own home outside of the historical work around of cobbling together a "clearance" (aka approval) process with registration and listing.

Remove reference to 1976. No other country in the world assumes that all class II products legally marketed before 1976 are suitable as reference products for performance standards.

Harmonize EU ISO 13485[7] requirements with the US quality system regulations. FDA does not have the resources to do biannual inspections of all class II manufacturers and lacks many authorities outside the United States. Use required third party manufacturing quality systems to supplement FDA inspectional authorities. Compliance predictability removes potential impediments to innovation implementation.

Do not require comparisons to predicate devices where performance standards are a better alternative. In those cases predicates should not be allowed and clearance should rely on accepted standards. Confidence in the evidence for clearance fosters acceptance of innovation.

Risk reclassification should be re-engineered to become a process that is applied routinely to keep the regulatory requirements up to date with current science.

Humanitarian device exemptions (HDEs) should be split into class II and class III products. Orphan unmet medical need are not synonymous with high risk. The potential for HDEs to foster innovation has not been reached because of the regulatory burdens of the program.

Refine the methodology for collecting clinical performance data across the product life cycle and across product generations. Unlike drugs where large, blinded placebo controlled trials are often needed to detect drug effects, device performance, and failures are often more directly observed. Health care providers and users benefit from precision in the relevant estimates relevant to the safe and effective use tracked over the product's life cycle.

Refine the safety information collected about devices and tailor the information to the specific performance characteristics of specific devices.

[7]The international device quality systems manufacturing standards. These are similar to the FDA Quality System Regulations.

Although class II "tool claim" products do not have clear off-label use (since there is barely a description of on-label use), collect the information about clinical outcomes and safety across the uses. Do not clear a surgical mesh just because it is "fit for use" without a plan to find out how the product is used and where it performs well and poorly.

SUMMARY AND CONCLUSIONS

There are many things in the current life-cycle regulatory framework that FDA "gets right." Device marketing requirements are and should be risk based. Class II reviews are multidisciplinary and science-based and assess the requirements determined by the use of the product in the clinic. Manufacturing quality systems for a given product are tailored to the complexity and risk of that product. Attention to corrective and prevention action programs creates iterative product improvements. Recognized standards and product guidances are integral parts of the device regulatory framework. CDRH is effective in assisting small businesses and promoting innovation.

Changes in the 510(k) process potentially would better foster innovation and ensure confidence that the process results in safe and effective medical devices. Class II approvals should no longer reference preamendments (1976) products. Class II approvals should be based on objective performance criteria that ensure safe and effective use, when appropriate based on comparison to predicate devices recognized as meeting those standards. "Tool claims" are essential for the practice of medicine but some of these products would be more safely used if their actual use were better understood. Manufacturers should still be able to modify their devices when a new 510(k) is not required, but they should send the device equivalent of a PMA CBE (changes being effected) to the file at FDA so that FDA could request more information when appropriate. Class II device manufactures should be required to provide ISO 13485 certification for their manufacturing quality systems.

No review of FDA performance is complete without a comment on FDA resources. CDRH should have the resources to make classification reviews an on-going and dynamic process, complete a guidance document for every product classification, create an oversight process for a mandatory ISO 13485 certification by third party inspectors, develop a gap-closing process with CLIA for oversight of lab based tests that is streamlined and risk based, and continually seek proposals on how to maintain a vibrant and innovative medical device development community.

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