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Research Article

Regulatory Assessment of Premarket Approval of Medical Devices in US and EU

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ABSTRACT

The demand for medical devices globally has raised the attention of government regulatory bodies to ensure the safety and effectiveness of these products. Developed markets, such as the United States and European Union, have set up well-established regulatory systems for medical devices, which have consistently been amended to accommodate the changing requirements of safety and the trend of globalization. The way in which devices are regulated in the European Union is very different from that of United States, especially in terms of the clinical data required for premarket approval. This has introduced significant differences in time-to-market approval for both United States and European Union, particularly in the case of high-risk Class III and Class IIb implantable devices. Systems for approving new medical devices must provide pathways to market important innovations besides ensuring that patients are adequately protected. To achieve these goals, the United States and the European Union use a combination of premarket testing and postmarket vigilance but with some marked contrasts in their approaches. Features of both environments require reform, as well as continuing research to assess policy changes which will benefit device manufacturers to develop devices which can be marketed both in US and EU simultaneously.

Keywords: Medical devices, United States, European Union, Regulations.

INTRODUCTION

Millions of patients worldwide depend on an ever widening array of medical devices for the diagnosis and management of disease. A frequent point of comparison for device regulation in the United States is regulation in the European Union. The current environment is rife with debate calling for FDA and EU reform of the regulatory process for medical devices. However, the EU system has drawn criticism for conflicts of interest in its evaluation process, and a recent recall of a popular silicone breast implant that was approved only in the European Union has reinforced European concerns about the clinical evaluation of high-risk devices. The regulatory approach taken by the FDA in the US differs fundamentally from the approach taken in the EU. While the US utilizes a centralized approach through the FDA, the European CE (Conformité Européene) marking process is much more decentralized. As policy makers in the United States and Europe weigh these critiques, it is an opportune time to compare the two systems and consider what evidence exists on the performance of each device-approval system[1].

History of premarket approval of medical devices

US

The FDA first received statutory authority to regulate medical devices as part of the 1976 Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act. Until that point, medical devices had no official premarket requirements and were subject to state-level oversight via consumer-protection statutes applicable to all commercial products. However, a public health crisis arose when the Dalkon Shield, an intrauterine device originally marketed in 1970 and used by millions of women in the US, was found to be associated with increased risk of pelvic inflammatory disease, sepsis, miscarriage, and death. As with all medical devices at the time, there was no premarket assessment of the Dalkon Shield's safety or effectiveness. After the Dalkon Shield was ultimately withdrawn from the market in 1974, the episode inspired Congress to centralize medical device regulatory power in the FDA.

The Medical Device Amendments enumerated three different regulatory classes of devices based on their risk to patients. Low-risk, or class I, devices (*e.g*., bandages, stethoscopes) are generally exempt from FDA review, requiring only registration with the agency and adherence to basic FDA standards about good manufacturing practices. Medium-risk, or class II, devices (*e.g*., blood pressure cuffs, peripheral vascular catheters) most often gain clearance for widespread use based on a finding of "substantial equivalence" to an existing marketed device. This process is commonly referred to as the 510(k) pathway after the applicable section of the Federal Code. A finding of "substantial equivalence" means that the device shares pertinent characteristics with another marketed device that has been safely used by patients and, therefore, does not require additional clinical testing to ensure its safety and effectiveness. The substantial equivalence standard for class II devices has been

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criticized in recent years for failing to adequately assure device safety and effectiveness. The recent recall of metal-on-metal hip implants has served as an example of the danger in allowing new devices to gain 510(k) clearance based on similarity to previous versions, not based on evidence of safety and effectiveness.

High-risk, or class III, devices — those which support or sustain human life, prevent impairment of human health, or present a potential, unreasonable risk of illness or injury—are generally reviewed via the premarket approval (PMA) process. Historically, the FDA has permitted select categories of high-risk devices to gain clearance through the 510(k) pathway rather than requiring PMA approval, a practice that has been criticized in recent years. The FDA has been working to update device classifications to prevent high-risk devices from gaining approval via the substantial equivalence standard, so fewer such devices should be on the US market in the future

The Medical Device Amendments established the standard of evidence for PMA review, authorizing the FDA to require "reasonable assurance of safety and effectiveness" for new high-risk devices. Similar to the FDA process for approving new drugs, the PMA process requires manufacturers to perform pre-clinical and clinical studies before a device can be marketed. The FDA was granted permission to request from a device manufacturer any data it considered relevant to providing reasonable assurance of safety and effectiveness.

In the subsequent decades, Congress continued to amend the Food, Drug, and Cosmetic Act to address concerns that over-burdensome regulatory processes were inefficient and preventing new medical devices from reaching the market in a timely manner. For example, while all new high-risk devices were originally required to be reviewed by an independent panel of experts, Congress amended the law in 1990 to allow the FDA to internally review PMA applications in cases in which such panels were not deemed to be necessary.

In the 1997 FDA Modernization Act (FDAMA), Congress required the FDA to work with manufacturers to determine "the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval. The FDA released a guidance document in 2002 that described how it intended to implement this "least burdensome" approach while still assuring device safety and effectiveness prior to marketing. The FDA permitted the use of non-clinical data (bench or animal testing) in place of clinical data in limited circumstances, and, when clinical data was needed, urged manufacturers to consider study designs other than randomized controlled trials and the use of surrogate endpoints to shorten study duration. The FDA also indicated that manufacturers could offer to formally collect safety and effectiveness data in the postmarket period to speed premarket review. Finally, the FDA recommended using "information that is available from earlier versions of the same device or from marketing experience with similar devices" as part of a PMA review[2].

EU

Until the 1990s, each member state had its own approach in regulating devices. To regulate a diverse and complex market and promote the "internal market" in Europe, new regulations, known as the *New Approach Directives*, were introduced by the European Council that defined the "Essential Requirements" to ensure devices' safety and performance. These requirements apply to all countries. Therefore, if a device meets the requirements and receives a CE mark in one country, it can be marketed in all member states. A CE mark certifies that a device is safe and functions according to the intended purpose described by the manufacturer. Under these directives, devices are categorized into four classes according to the degree of risk associated with their intended use.

Similar to those of the United States, Europe's evidence requirements for market authorization increase with the degree of risk associated with the device. Manufacturers of low-risk devices (Class I) are required only to self-declare conformity with the Essential Requirements to a national "Competent Authority," such as the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom. More moderate-and high-risk devices (Classes IIa, IIb, and III) require a combination of clinical and non-clinical data on the device being evaluated. If available, data for an equivalent device already on the market may be submitted. Although clinical studies are generally requested for high-risk Class III devices, the evidence requirements are vague, not available to the public, and non-binding for manufacturers and studies need not be randomized. For manufacturers claiming similarity to an existing product, a comparative literature review typically suffices.

Once a device is on the market, manufacturers are required to report all serious adverse events to the Competent Authorities. In Europe, this information is collated into a central database, the European Databank on Medical Devices (Eudamed). In addition to vigilance information, Eudamed contains data on manufacturers; certificates issued, modified, suspended, withdrawn, or refused; and clinical investigations. The use of Eudamed has been mandatory since 2011. Postmarket studies also may be required if a device's medium-or long-term safety and performance are not known from previous use of the device or when other postmarket surveillance activities would provide insufficient data to address risks[3].

Mandate

The FDA was given a mandate to provide reasonable assurance of the safety and effectiveness of medical devices due to public outcry over adverse events. Thus, the FDA may consider the severity of the disease and available alternatives when evaluating high-risk devices. By contrast, the E.U. system is part of a framework for commerce, which originated as a means of streamlining trade and coordinating manufacturing, safety, and environmental standards within the European Union.

Centralization

Central coordination in the United States allows postmarket phenomena in one generation of devices to inform later applications and study designs. A central registration system also provides publicly searchable

Classification of Medical Devices:

U.S (Risk based)	E.U (Risk based)
1.Classification Class I Class II Class III	1.Classification Class I Class II a Class II b Class III
2. Description Class I Simple in design and manufacture and have a history of safe use. E.g. Tongue depressors, crutches, and scalpels. No to negligible risk Class II More Complicated with Higher level of Risk. E.g. Endoscopes, infusion pumps, and condoms. Low Risk Class III Potential, unreasonable risk of illness or injury to the patient. E.g. Coronary stents, defibrillators, and tissue grafts. Medium and High risk. [4]	2. Description Class I Simple in design and manufacture and have a history of safe use. Little risk to the Human body. E.g. Reading glasses, thermometers, and examination gloves. No to negligible risk Class II a Short-or long-term use of devices. Low risk to the human body. E.g. Digestive catheters, infusion pumps, and powered wheelchairs. Class II b High risk to the human body. E.g. Respirators, dialyzers, and orthopedic implants. Medium Risk Class III Long-term, surgically invasive devices that may endanger the patient's life E.g. Coronary stents Include special Class III (AIMD) devices which requires source of energy to function. E.g. Pacemakers, defibrillators, cochlear implants High risk. [5]
3. Pre Marketing Requirements Class I Most Class I devices are exempt from premarket notification and/or good manufacturing practices regulation, although some general controls apply e.g., Device registration and listing, labeling regulations. Class II Required to clear premarket notification 510(k) requirements. In rare cases clinical studies are required for a 510(k) submission. May be subject to other special controls, such as special labeling requirements and mandatory postmarket surveillance. Class III Most stringent requirements. Premarket application (PMA) is required which includes evidence from prospective, randomized control trials.[6,7,8]	3. Pre Marketing Requirements Class I Manufacturers are allowed to declare conformity with the Essential Requirements. Class II a Manufacturers are required to submit a dossier of relevant supporting literature (clinical and nonclinical). Class II b Declaration by the manufacturer that the product conforms with the provisions of the Medical Devices Regulations and the relevant essential requirements Class III Clinical studies are recommended but most are non-randomized and single arm (focused on demonstrating safety). Requirements are variable across notified bodies.[9]
4. General time to approval Class I - Varies. Class II - 6 to 12 months. Class III – More than 12months	4. General time to approval Class I – Approval is not Required. Class IIa – 1 to 3 months Class II b - 3-6 months Class III - 6-9 months
5. Postmarket Requirements Reports of device safety and performance problems are mandatory for manufacturers. They use the MAUDE (Manufacturer and User Facility Device Experience database), MedSun (Medwatch adverse event reporting program), and Medical Device Surveillance Network (network of facilities collecting data on device-related problems). Postmarket studies are required for certain devices, particularly those in Classes II and III.[10]	5. Postmarket Requirements Manufacturers are required to implement a postmarket study and/or vigilance program according to national requirements, which includes reporting serious incidents to the relevant Competent Authority. Reports are synthesized in the Eudamed database.

Approval of Medical Devices:

Prominent Points of Comparison between the United States and European Union for Approval of Medical Devices.[11, 12, 13]

System Feature	United States	European Union	Potential Implications
Mandate	Oversight of public health	Device safety (overseen through Competent Authorities), device approval (through Notified Bodies), and facilitation of trade	May influence dealings with industry clients, and attention paid to balance between effectiveness and risk of safety concerns
Centralization	Oversight of all device regulation by the FDA	Directives outline processes carried out by Competent Authorities and Notified Bodies	Standardization and coordination of premarketing and post marketing evaluation are theoretically simpler and easier to enforce in the United States
Data requirements	Reasonable assurance of safety and effectiveness for approval of high risk devices, "substantial equivalence" for 510(k) clearance	Generally performance-based analysis, requiring proof that device works as intended	E.U. assessment made by manufacturers and Notified Bodies; provides less insight into clinical end points for high-risk devices
Transparency	Proprietary limits with public reporting of premarketing review of approved devices, recalls, and adverse events	Review of Notified Bodies not made public; postmarketing data shared among Competent Authorities but not with the public	Greater public access to evidence in the United States
Funding	Combination of federal appropriations (80%) and user fees (<20%)	Funding of Competent Authorities variable among countries; Notified Bodies paid directly by sponsors	Notified Bodies may be vulnerable to conflict of interest with industry client; the FDA may be influenced by changes in federal funding and political climate
Access	Clinical premarketing testing of high risk devices delays patient access to these devices (no differences for low and moderate-risk devices)	E.U. patients may have access to certain high-risk devices sooner than in the United States, subject to limitations by payers	E.U. patients have faster access to certain devices, but these products are marketed with less rigorous proof of effectiveness and may have a greater chance of later-identified adverse events

listings and databases of adverse events and postmarketing reports, which are useful to independent researchers evaluating specific devices.

Data Requirements

In the United States and the European Union, data requirements for high-risk devices can differ substantially. Devices that are cleared through the 510(k) process in the United States generally do not require clinical trials, which remain a point of substantial controversy. Studies in the European Union regarding the premarket features of devices that are subject to recalls have proved impossible to conduct.

Transparency

The FDA has several mechanisms for making its decision-making process accessible, even though much of a sponsor's application for a new device may remain proprietaryAt the time of approval of high-risk devices, a "Summary of Safety and Effectiveness Data" provides the justification for approval as well as discussion of adverse events.

Funding

In the United States, user fees account for less than 20% of the budget for the medical-device approval process and the government supplies the remainder. Relying on centralized funding subjects the FDA to resource limitations, particularly in post marketing surveillance. In the European Union, the funding of Competent Authorities varies with different combinations of public support and fees levied on manufacturers or Notified Bodies, and this variability may exacerbate differences among the resources focused on device safety in each country.

Access

Patients in the European Union have access to some new, complex technologies earlier than patients in the United States (in some cases, several years earlier), though precise estimates vary among reports. In the United States, truly new but high-risk devices may be available at an early stage only through a humanitarian exception or as part of a clinical trial, and in both cases conditions of use include oversight by institutional review boards and typically post approval studies evaluating outcomes.

However, differences in timing are related to the need in the United States to conduct clinical trials for high-risk devices. Although E.U. patients may have earlier access to some devices, they also face the risk that subsequent studies will show no benefit to the new device or reveal important harms from adverse events that did not emerge from the premarket review[14].

CONCLUSION

Regulatory systems for medical devices have an important role in supporting market access to technological innovations while duly protecting the public's health. In order to meet this aim, robust premarket assessment and postmarket vigilance are required. Both the United States and Europe have recently introduced or are in the process of establishing reforms to meet this end. Such initiatives should be implemented in a timely manner, though additional actions will be required to enhance the reforms' effectiveness. More research is needed to assess the ongoing performance of regulatory approaches for devices.

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