

Should Medical Devices Be Regulated as Rigorously as Drugs?

THE “PRO” SIDE

The term “medical device” applies to a broad set of product categories, ranging from simple, low-risk devices, such as tongue depressors, to complex, high-risk devices that are implanted or sustain life, such as drug-eluting cardiac stents, implantable pacemakers, and deep-brain stimulators. Such devices are intended to be used for diagnosis, prevention, monitoring, treatment, or alleviation of disease and do not achieve their primary intended action by pharmacological, immunological, or metabolic means.¹ At present, medical devices are increasingly integrated into pharmacy practice. For instance, with the availability of medication delivery systems (e.g., insulin pumps) and combination products (e.g., drug-eluting stents), pharmacists are in a position to provide education, to assist in implementing appropriate adjunctive pharmacotherapy when needed, and to support decision-making about where and when to use the devices.² Moreover, pharmacists may also be involved in choosing medical devices during the procurement process, monitoring the efficacy of medical devices once they are in use, and managing and reporting adverse events associated with these products.³ Therefore, it is important for pharmacists to have a good understanding of the regulation of medical devices.

The regulation of medical devices varies greatly around the world. Some countries, such as the United States, countries within the European Union, Japan, and China, have adopted a tiered, risk-based approach. In these countries, regulatory departments prioritize the limited resources available, focusing regulatory measures on high-risk products. As such, various products are subject to different standards and enforcement activities, depending on the level of risks, as determined by the regulatory authority. In other areas of the world, regulatory requirements for premarketing assessment of medical devices are minimal or low. Moreover, regulatory systems may also differ vastly in terms of their classification of medical devices, risk-based regulation, and premarket evaluation, which results in different levels of assurance concerning safety and effectiveness.⁴ For example, one study showed that medical devices approved first in the European Union, which was known to have a less stringent regulatory system for these products, were associated with a greater risk of postmarketing safety alerts and recalls than products approved first in the United States.⁵

Many clinicians and patients believe that current methods of regulation and enforcement within and across countries are not fit for the purpose of safety assurance.^{6,7} The medical device market has become globalized, and the number of reports about adverse events associated with medical devices leading to serious complications or even death is on the rise. There have been reports of medical devices being brought to market without sufficient independent assessment of safety and efficacy to safeguard patients.^{8,9} Even in the United States, with its relatively strict regulatory environment, more than 80 000 deaths and 1.7 million injuries have been potentially linked to medical devices during the past decade.¹⁰ In April 2019, the US Food and Drug Administration finally stopped the sale of vaginal mesh (which had been approved in 2002 as a class II “moderate risk” medical device) after tens of thousands of patients reported serious complications, including intense pain and bleeding, after implantation.¹¹ The stringency of the approval process for higher-risk products, which may require only bench-testing data and perhaps some clinical study, and the delay in responding to new findings about adverse events have been repeatedly questioned.¹²

There have been calls for more robust regulatory measures for medical devices, but objections to tougher oversight have been intense. Some manufacturers argued that more rigorous regulations will increase the costs of development, manufacturing, and service for the industry and ultimately for health care providers and patients, limiting access to the devices themselves and to innovative development.^{13,14} This debate continued, without any major impact on the regulatory systems, until recently, when the results of a global investigation into medical device misadventures revealed numerous cases of malfunction, injury, or even death associated with devices that had been approved for sale by regulatory authorities.¹⁵ It was then concluded and recognized that health authorities around the world had failed to protect patients from poorly assessed medical devices. In light of increased public attention and concerns, some countries have finally stepped up their regulation of medical devices. In Australia, the Therapeutic Goods Administration has announced an action plan that strategically aims to improve how new devices get to market, to strengthen the postmarket monitoring of devices, and to provide more information to patients about the devices they use.¹⁶ Other countries, such as the United States, France, Canada, Italy, Germany, the United Kingdom, the Netherlands, and India, have also announced new actions and measures in attempts to close the gaps in the risk management of medical devices.¹⁷

Pharmacists have come to appreciate the importance to our patients of stringent regulation through lessons learned from the history of pharmaceutical regulation. Sadly, this history reminds us that laws and regulations protecting public health are rarely proactive, but instead are usually enacted following public health disasters. The sulfanilamide tragedy of the 1930s was the trigger for enactment, in 1938, of the US *Food, Drug and Cosmetic Act*.¹⁸ The thalidomide disaster of the 1960s prompted governments around the world to raise the safety standards for pharmaceuticals.¹⁸ The rofecoxib incident of the early 2000s led to calls for the reinforcement of pharmacovigilance to identify rare and severe adverse events as early as possible.¹⁹ Given what is known about how previous health disasters have shaped the current regulatory landscape for pharmaceutical products, the need for a system of independent assessment of medical devices by regulatory agencies, one that continues to evolve and develop according to technological advancements and patients' needs, is indisputable.

What is worthy of further discussion is the repositioning of regulatory systems for medical devices and how to achieve the goals of protecting and promoting public health and optimizing clinical outcomes for individual patients.²⁰ Historically, the fundamental job of regulatory agencies was to protect the general public from the "harm" of medical devices by keeping substandard and/or unsafe products off the market. However, the vast and rapid development of medical devices and the increasing needs of patients have shifted the paradigm toward a more proactive role for regulators. These agencies are now expected to promote public health by also facilitating innovations so that safer, more effective, and more economical medical devices can become accessible as quickly as possible. These goals are challenging, given the advancement of new technologies and the increasing complexity of product design. To address the challenges, the discipline of regulatory science should be better applied to support scientific regulation of these products.²¹ Apart from developing new tools, methodologies, standards, models, and approaches to assessing the efficacy, safety, quality, and patient benefits of medical devices, there should also be a focus on alignment among industry, research institutes, payers, consumer advocacy groups, and other stakeholders, so that capacity can be built across different sectors for the development, implementation, and effective execution of guidelines and care pathways. Regulatory science also emphasizes the collection and leveraging of real-world data for regulatory decision-making, especially for high-risk medical devices. For this, pharmacists, as part of the multidisciplinary team supporting better regulation of medical devices, should have an increasing role to play in clinical vigilance, through monitoring medical device efficiency and managing and reporting any adverse events associated with such devices.

In summary, a reliable regulatory system and greater regulatory transparency about medical devices are important to protecting public health and the health of individual patients. Pharmacists have a growing role to play in supporting the scientific regulation of medical devices.

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THE “CON” SIDE

*Perfection is achieved, not when there is nothing more to add,
 but when there is nothing left to take away*
 —Antoine de Saint-Exupéry, *Airman's Odyssey*

Around the world, the regulation of drugs is currently more rigorous than the regulation of medical devices, and at the jurisdictional level, the United States (US) has more stringent regulation of medical devices than the European Union (EU). However, this situation is about to change. In 2020, in response to the outcry about the notorious PIP breast implant scandal that occurred in France in 2010, the EU will be implementing a new medical device regulation, which will require more extensive clinical evidence than is now the case.¹ The company implicated in the scandal produced about 2 million sets of silicone breast implants over a period of 20 years using unapproved materials; these implants had abnormally high rates of rupture, and 30 000 French women were advised to have their implants removed.² Clearly, more safety assessments are needed, but medical device regulation will need a unique approach, different from that applied to drug regulation.

In the context of regulation, there are distinct differences between drugs and medical devices. The history of drug and medical device regulation in the US is a good example to elucidate these differences. In that country, the Food and Drug Administration (FDA) is the federal regulatory agency for both drugs and medical devices. The present drug regulatory system began in 1938 in response to the notorious Elixir sulfanilamide tragedy of 1937, which caused mass poisoning and more than 100 deaths.^{3,4} Before 1938, animal testing and premarketing clinical

studies were not required by law, and the company responsible for this tragedy performed none.⁴ The *Food, Drug and Cosmetic Act*, enacted in 1938, was the first step in making animal safety tests compulsory; with significant amendments enacted later, extensive clinical data evaluations to demonstrate the safety and efficacy of new drugs became a requirement for FDA approval.^{3,4} In contrast to this 8-decade history of drug regulation, the first clear regulation of medical devices in the US occurred in 1976, driven by rapid innovations in medical technology that convinced FDA officers to review certain new devices for premarketing safety and efficacy.³ In the 1960s, the argument was made that several medical devices, such as contact lenses and copper-7 intrauterine devices for contraception, should be regulated as “new drugs”, and FDA officers soon recognized that a clearer definition and a distinct regulatory system were required for medical devices, to avoid the unnecessary costs of regulation for medical devices with no obvious adverse effects.³ The central principle behind the 1976 amendments for medical devices was that “No single form of regulation, such as drug-like premarket approval, would fit all medical devices.”³ Therefore, medical devices were to be regulated differently.

Unlike the situation for drug regulation, which requires that rigorous clinical trials be applied to virtually all new drugs (except drugs for emergency use and orphan drugs used by small numbers of patients),⁵⁻⁷ not all new medical devices require clinical data. New devices are first classified according to their level of risk. In the US and the EU, 3 classes are used, with class I having low risk (e.g., dressings and gauges) and class III having high risk (e.g., heart valves and cardiac pacemakers). The Australian regulatory authority, the Therapeutic Goods Administration (TGA), has specified an additional class for active implantable medical devices (AIMDs), which also carry high risk; examples include implantable defibrillators and cardiac pacemakers.⁸ No clinical data are required for class I devices, whereas all class III and AIMD devices require clinical trials.^{7,8} Within class II, clinical evidence is required only for those devices having medium risk.^{7,8} To apply the same standard of regulation to all medical devices as is currently applied to drugs would be to suggest that devices such as dressings and gauges require clinical trial evidence similar to that required for a new class of medicines. Such regulation would involve unnecessary costs and inappropriate use of resources (on the part of manufacturers, regulators, and hospitals/patients). Instead of imposing additional clinical evidence requirements for low-risk devices, perhaps it would be better to invest effort in scientific evidence and expert review processes to ensure accurate identification of low-risk devices.

Before 2017, the clinical evidence requirements for class II devices differed between the US and the EU, with US regulation being more rigorous. About 75% of class II devices in the US required clinical evidence, whereas manufacturers in the EU were exempt from the requirement for clinical data if the devices had substantial similarity to previous “predicate” devices.⁷ The strict US regulations prevented the outcry about PIP breast implants

that occurred in the EU from extending to the US. Medical devices introduced in the EU earlier than in the US have also shown higher risk of postmarketing safety issues.⁹ However, the safety risks of medical devices are not necessarily directly associated with the safety and efficacy of the products themselves. One study compared the factors contributing to adverse events between medicines and non-AIMDs, and demonstrated distinct causes between these 2 types of adverse events.¹⁰ User challenges, design problems, and lack of effective training were identified as 3 major causes of adverse events with medical devices, but all of these are difficult to evaluate in premarketing clinical trials.¹⁰ Imposing new and more burdensome clinical trial requirements to evaluate the safety and efficacy of certain medical devices may not be as effective as implementing strategies such as increased user training and better customer service.^{10,11} Rigorous evaluation of medical devices is needed to minimize the risk of harm to users; however, such evaluation should be conducted by experts who can distinguish data that are essential for safety and effectiveness evaluation from data that are “nice to have”.¹¹ Furthermore, the advent of digital medical devices poses new and unique challenges to regulators, including cybersecurity risks.¹² These devices include stand-alone software, such as electronic health record systems, or software incorporated into various types of equipment, such as blood glucose monitors and computed tomography scanners, which can be vulnerable to cyberattacks leading to malfunction.¹² Assessment of cybersecurity risk cannot be evaluated by the FDA alone through traditional means of safety evaluation (e.g., clinical trials); rather, it requires transparent reporting of cybersecurity features and continual collaboration among regulators, manufacturers, health care providers, cybersecurity researchers, and government agencies.¹²

Excessive regulation could also pose more harm to the medical device industry through direct impacts on patients. It has already been predicted that the new EU medical device regulation will incur an additional 10%–15% in the cost of medical device development, which will be reflected in higher sale prices.¹ This regulation will also lead to higher financial risks for small and medium-sized companies, which constitute most of the medical device industry. For example, in Germany, 80% of medical device companies are small or medium-sized.¹ Increasing the approval burden will extend the product development cycle, cost, and approval time, making investments unattractive and possibly driving the industry to shift resources to improving existing products rather than generating truly innovative ideas.¹¹ FDA data have shown that applications for breakthrough approvals are low.¹¹

The primary goal of regulating medical devices is to ensure their safety and efficacy, yet it is also important to encourage innovations to bring benefit to patients. Given the distinct differences between medical devices and drugs, regulatory authorities need to take a unique approach to the regulation of devices, one that focuses on balancing the evaluation of safety and efficacy with innovation, rather than adopting the models of rigorous assess-

ment that are used for drugs. Studies investigating current medical device regulation have identified several key issues: lack of transparency in reporting the reasons for medical device safety alerts and recalls,¹³ lack of regulation of user behaviour,¹⁴ lack of high-quality postmarketing surveillance,¹⁰ and lack of incorporation of real-world evidence into regulatory decision-making.¹⁵ Improvements to medical device regulation are needed, but the simple approach of applying rigorous regulation, as is the case for drug regulation, will not be the solution.

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