The US Food and Drug Administration Premarket Approval Process and the 515 Program Initiative

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The US Food and Drug Administration (FDA) regulatory process, in particular the regulation of cardiovascular devices, is not understood by most clinicians. Within the FDA, cardiovascular devices are regulated through the Circulatory System Devices Panel, one of 18 review panels of the Center for Devices and Radiological Health Organization. Dr Rathi and colleagues1 are to be commended for drawing attention to the regulatory process for cardiovascular devices and providing their perspective on how best to provide that cardiovascular devices are safe and effective.

Medical devices are classified according to the regulatory controls necessary to “provide reasonable assurance of their safety and effectiveness.”2 Class I devices (such as the manual stethoscope) do not require premarket review by the FDA. Class II devices require premarket notification of the FDA, through the 510(k) process, with the definition of general controls plus special controls that are developed specifically for that device; these special controls may include biocompatibility, bench, and animal testing. Class III devices cannot be classified into class II based on the conclusion that insufficient evidence exists that general and special controls are available to provide reasonable assurance of safety and effectiveness, and the devices are considered to be life sustaining and/or life supporting, of substantial importance in preventing impairment of human health, or presenting potential or unreasonable risk of illness or injury. Class III devices require a premarket approval (PMA) application process that often includes prospective, randomized human trial data that may be reviewed by an expert panel prior to final approval for marketing.3

The classification of a device remains a critical aspect of the path to approval, because the regulatory process for class II is much less extensive, time-consuming, and expensive than that of a class III PMA device; the class II device only needs to be demonstrated to be substantially equivalent to a predicate device and does not usually require clinical study to be approved through this 510(k) process. When these 3 classes were established by a 1976 amendment to the Federal Food, Drug, and Cosmetic Act, a number of class III devices that were already on the market were allowed to continue to be available as Class I or II devices on a temporary basis. Also known as preamendment class III devices, they were allowed to be marketed, and new substantially equivalent devices could be approved for marketing under the 510(k) process, pending final call for PMA or reclassification to class I or II. For various reasons these devices have been slow to undergo final classification. This process was accelerated in 2009, when the FDA established the 515 Program Initiative to address the remaining devices, many of which were cardiovascular. Currently only 2 cardiovascular devices await final classification.4

Rathi and colleagues nicely describe the 515 Program Initiative and in particular the regulatory history of the Impella device. The Impella had been marketed based on a predicate class III 510(k) device, the non-roller cardiopulmonary bypass pump, despite the fact that the Impella represented a different technology (a catheter-based axial pump) that was employed for a different clinical purpose (temporary ventricular assist as opposed to cardiopulmonary/circulatory bypass). The Circulatory System Devices Panel concluded unanimously (13 to 1, with 1 abstention) that nonroller bypass pumps used for cardiopulmonary or circulatory bypass should be reclassified as class II. However, the panel strongly recommended (10 to 3, with 1 abstention) that the Impella should be class III; this was based on insufficient evidence to determine general and special controls that would assure safety and effectiveness for the indication of temporary ventricular support. The panel recommended continuing postmarket studies and analysis of preexisting data to support a PMA application. The PMA was submitted and approved, so that the Impella has been marketed as a class III device since March 2015.

The authors state that approval of the Impella “raises important questions about whether robust clinical evidence will be generated for preamendment high-risk devices through the 515 Program Initiative,” citing that large, real-world assessment is unavailable and that “problematic historical evidence” would be considered.1 Their caution is warranted, but one must remember that review panels and the FDA deal with imperfect data.

I served as temporary chair of the Circulatory System Devices Panel that considered reclassification of nonroller pumps (including the Impella), and I have served as a panelist or chair in 6 panels to consider reclassification in the 515 Program Initiative since 2011. Although a panel vote is advisory, a clear majority of the panel generally determines FDA action. As the panel considers any PMA device, it wrestles with the balance of safety and effectiveness, and we often wish the data could offer more definitive guidance. The panel’s job is even more challenging when considering a device that is already in common use. As the panel deliberates how to classify a class III 510(k) device, we are assured by the FDA, and we state for the record,5 that our vote to maintain class III and require the PMA process will not result in a withdrawal of potentially life-saving devices that are
already on the market. We are also assured that the PMA process for the preamendment devices will be the least burdensome possible. On the other hand, we are sending a clear message that we expect that similar devices, not already marketed, will only be approved for marketing after thorough consideration through the standard PMA process.

Panel deliberations, at their core, are based on protecting the American public within the context of determining reasonable assurance of safety and effectiveness. The panel critically assesses data presented by both the FDA and the device sponsor. The medical, scientific, and statistical expertise assembled allows for rigorous consideration of the data presented. Our deliberation is enhanced greatly by the participation of nonvoting panelists representing consumers, industry, and most important, patients; these individuals provide diverse perspectives that complement the panel’s review of the statistics and science. To further keep us mindful of the population we serve, each meeting has an open public comment portion within which we hear from clinicians, patients, families, professional organizations, and other advocacy groups, among others. Often these varied perspectives inform our discussion in a profound way.

After the FDA receives panel recommendations, the regulatory process proceeds, independent of further input from the review panel. In the case of the Impella, did the FDA get this right?

I believe so. There was no interruption in access to the device while the manufacturer submitted a PMA. Based on analysis of data from clinical trials and registries, and with the expectation of further prospective study, the device was approved for the indication for partial circulatory support for periods up to 6 hours, generally in the setting of high-risk percutaneous coronary interventions. It would have been unreasonable to expect new, randomized, prospective studies of this device, and it would have been unfair to withhold this therapy pending such study. The precedence of the Impella device provides reassurance that similar PMA approval can be achieved for other preamendment class III devices such as the automated external defibrillator.

Although I agree with Rathi et al that the data for approval were imperfect and postapproval trials and registries have limitations, I am gratified that the authors recognize that the FDA has a “difficult task of requiring meaningful evidence for approval without placing undue burden on manufacturers” in cases for which a device is already in widespread use. Much more important than the consideration of burden on the manufacturer, though, is continued availability of potentially life-saving technology. We must not be so critical of the data available that we withhold potentially life-saving devices, from the physician and the patient, that are already in clinical use.

ARTICLE INFORMATION
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REFERENCES