Separating Regulatory and Clinical Standards

Understanding the FDA device approval process and the difference between data from premarket and postapproval trials to make informed clinical decisions.

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The practice of medicine is becoming increasingly complex with each passing year. Specialty physicians are not only expected to manage complex disease but to do so within the confines of the types of medications and procedures approved by health care institutions and payors. Developing value-based care pathways is crucial in such a restricted environment. Nowhere is this more pressing than in the treatment of vascular disease.

Although health care providers have furthered their education on disease management, procedures, and devices through multiple educational modalities such as peer- and non–peer-reviewed articles and continuing medical education presentations, it is more complex to extend such education to nonphysicians or health care providers. FDA regulations mandate that medical device companies only market or provide education on data that is on-label. Health care institutions may even go further to try to limit device use beyond the instructions for use and considered "off-label." Both institutions and physicians need proper understanding of the regulatory complexities and why the standard of care for a particular treatment may not be on-label. At the other end of the spectrum, physicians and providers should appreciate the need to critically investigate and understand the data generated to support their decision-making process.

HOW DEVICES GAIN APPROVAL BY THE FDA

Currently, medical devices can be approved by the FDA via premarket approval (PMA) trial data or the 510(k) "predicate-based" pathway. The 510(k) pathway approval is considered when the device is believed to be substantially equivalent to a preexisting FDA-approved device. At present, the majority of so-called new devices gain approval through this pathway, some without any human testing; however, many devices in the cardiovascular space are class III devices and typically require PMA. Some lower-risk devices, however, can be approved without human testing, and in fact, it is estimated that 10% to 15% of all 510(k) approvals require human testing.[1] Another troublesome fact is that the predicate may have been withdrawn after approval for poor performance or safety issues, but it can still be utilized as essential equivalence because it was approved at some time. Thus, physicians should use a critical eye when evaluating new devices and data.

Once approved or cleared for marketing by either pathway within the United States, the device can legally be utilized by physicians to treat any condition the physician deems medically appropriate. This is distinctly different to marketing the device, because device manufacturers can only legally market the device for the on-label indication.[2]

Obtaining New Indications

The FDA recognizes that the use of a device beyond the on-label use may in fact become the standard of care for some devices.[3] This right of physicians to practice medicine beyond the on-label indication, without FDA approval, is considered legal under Federal law. However, in order to add new indication(s) to the existing FDA-approved indication, manufacturers are required to submit new clinical data, commonly in the form of clinical trials, for the specific vascular indication(s) being pursued. Physicians utilizing a device "off-label" walk a fine line between FDA goals and the prerogative of physicians to use their professional judgment to best treat their specific patients.

HOW CLINICAL DATA ARE GENERATED

It is important to understand the difference between data generated from FDA approval trials and postapproval data to make optimal clinical decisions. A thor-

ough understanding of the types of research studies that generate data and their application in clinical practice is essential. Although an individual physician's personal experience may play some role in procedural decisions, most physicians will develop evidence-based treatment plans based on outcomes data. Device data are typically generated from PMA trials, predicate data trials (510[k] pathway), and postapproval data. The postapproval/postmarket data are reported in the form of case reports, single- or multicenter registries, and, rarely, randomized comparison trials.

For devices that have no predicate phase 1 safety trials, follow-up pivotal trials are performed to demonstrate efficacy and continued safety. Randomized data sets comparing the tested device to the current standard of care, with independent adjudication of results and safety, are considered optimal for generating level 1 data. However, registry data may suffice when a significant amount of high-quality historic data are available for comparison.

PMA Data

PMA data sets, especially in medical device trials, utilize highly specific predefined patient data sets and endpoints to control the most important variable(s) being tested. Typically, these trials enroll 150 to several hundred patients. An attempt to expand beyond the predefined initial data set (to include broader patient populations) requires increasing the sample size to thousands of patients, which could be cost prohibitive.

Current PMA trials are designed to prove the safety and efficacy of medical devices and to reduce the number of variables that may inadvertently and adversely affect the results. To limit potential bias, these trials are typically monitored by an independent organization as well as by a clinical events committee (CEC) and core labs. Core labs are independent adjudication entities that have quality assurance systems in place to eliminate bias and variability of interpretation and reporting of imaging data such as angiograms, axial imaging, ultrasound imaging, and wound imaging. This adjudication process eliminates both inter- and intraobserver variability, resulting in "clean" data.

With safety and efficacy as the key outcome measures, a typical PMA study in the femoropopliteal bed is usually limited to shorter lesion lengths and excludes variables such as renal failure, severe calcification, and disease within 1 cm of the ostium. Furthermore, because the FDA does not design these trials but merely responds to trial plans, each trial may have its own unique characteristics, such as definitions of patency, calcification, and lesion length.

Postapproval Data

After FDA approval, insight into the use of devices may further expand based on the data generated from a variety of studies, including case reports, single-center registries, industry-sponsored postapproval registries, and investigator-initiated trials that are commonly financed by industry through unrestricted educational grants. These postapproval data are often described as real-world data. However, these so-called real-world data are also considered a "messy place" from the perspective of seeking robust data and unbiased treatment outcome comparisons.[4] Postapproval data can be much less expensive to obtain because less rigor is required for data collection. These studies are also often performed without CECs or core lab adjudication of the data and without formal monitoring of the sites, which leads to less reliable results and conclusions.

Postapproval data sets provide access to larger numbers of patients and more accurately reflect the "real-world" practice of medicine. However, data sets without independent oversight have many shortcomings. In most research, trialists wish to emphasize the positive aspects of their data. However, emphasizing the positive may lead to imbalanced and biased data presentations. Assessing a particular technology in the real-world setting is very important, because these populations undergo most of the treatments. Postapproval studies must have predetermined variables and transparent definitions of the variables being evaluated. Post hoc analyses across subgroups often lead to an exaggeration of the true effect, especially from selection bias, if the tested patients are not consecutive. Comparison of like trials is very common but problematic. Often, the populations, definitions, and treatment environments can vary considerably, leading to inaccurate comparisons. This is even more common in postapproval trials that have inherent bias, and these comparisons are not fair or true comparisons and the scientific reliability is low.

SUMMARY

Regulatory trials are designed to meet "least burdensome" FDA approvals, typically with tightly controlled variables and a highly specific predefined patient population. *Least burdensome* is defined as a successful means of addressing outdated and unnecessary burdens in the FDA regulatory approach, which involve the appropriate investment of time, effort, and resources on the part of industry and the FDA. Although this process and these data have the potential to be imperfect due to various biases, the biases may be significantly minimized by involving independent safety monitors

and using source data adjudication by independent core labs. Well-done level 1 studies leading to FDA approval of devices for physician use is the first step in the approval process. However, caution must still be exercised for device utilization in the broader patient population. Postapproval data allow insight into outcomes in the broader patient population but are typically associated with selection bias and less robust data collection, leading to uncertain reliability. Comparing trials is problematic and should only be done with the utmost caution. Physicians are in a unique position to legally use approved devices in an off-label manner, but this must be done only after careful scrutiny of all available data prior to using these devices and treatments in order to achieve the most optimal patient-centered clinical outcomes. ■

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