Regulatory hurdles in bringing an in vitro diagnostic device to market

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We discuss the hurdles that developers and manufacturers of in vitro diagnostic devices face in obtaining regulatory approval to market their products in the US. A thorough understanding of medical device regulation and the early planning of a clinical and regulatory strategy are imperative in assuring successful and timely launches of new products. Finally, it is critical for manufacturers to establish a working partnership with the Food and Drug Administration to expedite their new product applications.

Manufacturers of in vitro diagnostic devices (IVDs) face numerous challenges in getting their products to market, one of which is obtaining clearance or approval from the US Food and Drug Administration (FDA). In recent years, times for product review have lengthened considerably. In addition, there has been an increasing burden on device manufacturers to provide not only supporting safety and effectiveness data, but clinical utility information as well. In contrast, European and Japanese regulatory agencies focus primarily on safety data to satisfy premarket review requirements, thereby speeding medical devices to market in those countries. This regulatory scheme permits effectiveness and utility determinations to be made by medical practitioners after product introduction and supports a highly competitive marketplace. Because of the increased time and effort involved in bringing a new product to the US market, some domestic manufacturers are initially marketing their devices overseas or moving their entire manufacturing operations offshore. There are indications, however, that the FDA is now moving to expedite product approvals. Manufacturers must develop expertise in medical device regulation, carefully plan a clinical and regulatory strategy early in the product development cycle, and work to partner with FDA in the product approval process if they are to reap regulatory success.

A new IVD typically involves the application of a novel measurement technology to a familiar analyte. For example, CK-MB, which was originally quantified after electrophoresis, is now measured with immunoassay techniques. First-generation immunoassay methods such as RIA have evolved into enzymometric and fluorometric methods; now, polymerase chain reactions are at the forefront of bioanalytical techniques. Some IVDs, however, consist of measuring new analytes by either an established or a new technology. Although myoglobin and troponin have appeared in the research literature for years, these analytes are very new to the regulatory arena. Still other IVDs use existing technology to measure familiar analytes but in a new specimen matrix. In general, the less familiar the technology, analyte, or matrix to the FDA, the greater the regulatory burden on the manufacturer.

According to the Federal Food, Drug, and Cosmetic Act, a medical device is defined as an article to be used in the prevention, diagnosis, or treatment of disease. A device may be distinguished from a drug by not requiring chemical or metabolic activity to achieve its intended purpose.

The FDA classifies medical devices into three categories, based on the degree of control needed to ensure that the various types of devices are, and remain, safe and effective for their intended uses. Each category of medical device has different statutory and regulatory requirements with respect to premarket clearance (what is required to receive FDA approval) and postmarket surveillance (what is required to maintain regulatory compliance after approval):

Class I devices are considered to be low risk and are subject to general controls such as Good Manufacturing Practice regulations, facility registration, and device listing. Some examples of Class I IVDs are immunological test systems for serum triglyceride, uric acid, and prothrombin. Many Class I devices are exempt from premarket review by the FDA.

Class II devices are intermediate in terms of risk and are subject to special controls as well as all general controls. Special controls may be FDA guidance documents, device tracking, patient registries, and postmarketing clinical studies. Class II devices are subject to premarket scrutiny by the FDA, generally in the form of Premarket Notification submissions [510(k)].

Clearance of a Premarket Notification by the FDA requires the manufacturer to demonstrate that the new device is substantially equivalent to an existing, legally marketed device (the "predicate" device). Depending on the sophistication and intended use of the new device, such demonstration may consist of a simple analytical performance comparison or may involve a
more extensive demonstration of clinical performance. Examples of Class II IVDs include therapeutic drug monitoring assays, assays for drugs of abuse, and assays of cardiac enzymes. Finally, Class III devices are the most stringently regulated. As such, they are subject to all general and special controls, as well as premarket approval by the FDA. Class III IVDs include novel analytes and technologies for which no predicate devices exist. Product approval hinges on submission to the FDA of an extensive document known as a Premarket Approval Application (PMA). The data contained in the PMA are derived from both analytical performance testing and clinical studies—which are often large, multicenter trials that must be conducted according to the Good Clinical Practice regulations. These studies must be performed in the appropriate patient population of a statistically justifiable sample size. To receive approval, the device must be shown through rigorous statistical analysis to be intrinsically safe and effective for its intended use(s). Many PMAs are also scrutinized by expert advisory panels who make recommendations to the FDA, either to approve the application with or without conditions, or to deny approval. Examples of Class III IVDs include assays of tumor markers and gene probe tests for tuberculosis. (Recently, FDA and one of its advisory panels approved the reclassification to Class II of tumor markers used for monitoring previously diagnosed disease. This reclassification will not be effective, however, until a final regulation is published in the Federal Register.) It is critical for the developer or manufacturer of an IVD to establish which regulatory class is applicable and to ascertain the specific requirements that support FDA review of that device. Success depends on early consideration of these elements, preferably during the initial phases of product research. When developing new technologies to measure familiar analytes, it is important to consider whether the sensitivity and specificity of the new technology surpass that of currently accepted methodology. For example, gene probe tests for tuberculosis are far more sensitive and specific than current acid-fast staining and culture techniques. Are there new manufacturing or customer handling issues that need to be addressed? Again, in the case of gene probe assays, contamination is a primary concern in both manufacturing and customer use. Product development should be conducted such that optimization and nonclinical performance data generated at this phase can be used to support the regulatory submission. When the product in question is an assay for a new analyte, it is crucial to consider the population or disease state in which the device will be used. Is the device to be used in males or females? In children or adults? In what clinical condition(s) does the device have utility? For example, bone markers may be indicated for use in conditions such as Paget disease, osteoporosis, renal osteodystrophy, and bone metastases. How does the new analyte compare with other analytes or modalities that are used to diagnose or monitor clinical condition? What will be the intended use of the device—screening, diagnosis, monitoring, prognosis, or assessment of disease predisposition? Depending on what clinical condition and intended use are chosen, the regulatory requirements may be quite different. Manufacturers must weigh the existing clinical need for a product against the ease of obtaining regulatory approval. For example, although several assays of prostate-specific antigen have been approved for monitoring diagnosed prostate cancer, the regulatory requirements for a screening indication are much greater, and only one manufacturer to date has received approval to market its assay for prostate cancer screening. Finally, when the device measures an analyte in a new type of biological specimen, different issues arise. Urine, serum, and plasma are well-characterized matrices; sputum, cerebrospinal fluid, and whole blood are less well-characterized. New sample matrices raise questions as to proper specimen collection, handling, and storage, as well as analyte stability and potential interfering substances. FDA requirements for clearance of Class II and Class III devices are considerably different, which can affect the manufacturer’s approach to assay development. Class III devices require considerably greater monetary and human resources if they are to clear the regulatory hurdles. Also, the time to market is much longer for Class III devices. Some Class II devices may be reclassified to Class III if new questions of safety or effectiveness are raised by the use of the product. This may occur if (e.g.) the performance of the new device exceeds that of the comparison method or the product will be used to test for a disease that is a significant public health concern, such as tuberculosis. Reclassification of a device from Class II to Class III may substantially increase the investment required for the studies that must be conducted to gain regulatory approval. Testing for a Class III device may be more extensive, perhaps involving lengthy prospective trials at external institutions. Whereas an expenditure of $20,000 might be satisfactory for a Class II device, $400,000 might be required to obtain approval for a Class III device. Despite the enormity of the regulatory hurdles that must be cleared, some signs indicate that the FDA is in the midst of substantial internal reform. Manufacturers would be well-advised to take advantage of the initiatives that FDA has undertaken to expedite new product approvals. The agency is exhibiting a greater willingness to meet with industry to negotiate clinical study and submission requirements. Manufacturers should meet with the FDA early in the process, to familiarize the agency with the technology and to teach about the product’s clinical application. If the device is based on an unfamiliar technology, the manufacturer may also benefit by giving FDA an actual demonstration of the device. Agency comments and suggestions, along with the FDA’s general and product-specific guidance documents, are invaluable in assuring successful and timely launches of new products.

In summary, three key steps will help lower the regulatory barrier to commercialization of new IVDs. First, assess the clinical and regulatory requirements for the product while in the early feasibility phase. Second, partner with FDA so as to expedite their review of your product submission. Finally, don’t try to reinvent the wheel: Research the new-product strategies, successes, and failures of other manufacturers. With these key points in mind, IVD manufacturers can enjoy success in navigating the sometimes stormy regulatory waters and bringing new products to market.