Special Article

Food and Drug Administration Regulation of *in Vitro* Diagnostic Devices

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The Food and Drug Administration regulates the sale and distribution of laboratory devices under a statutory and regulatory framework that is unfamiliar to most clinical laboratory scientists. In this article we briefly describe the criteria that are used to classify and review *in vitro* diagnostic devices. We discuss the similarities and differences between devices that are not subject to premarket review, and those that are required to undergo either a premarket application or premarket notification [510(k)] pathway. We then discuss the methods that the Food and Drug Administration uses to assess the performance of *in vitro* diagnostic devices in the marketplace as a component of the total life cycle approach to medical device regulation. (J Mol Diagn 2005, 7:2–7)

In the United States, Federal regulation of laboratories performing diagnostic tests is performed by the Center for Medicare and Medicaid Services by authority of the Clinical Laboratory Improvement Amendments of 1988. Distribution in interstate commerce of *in vitro* diagnostic devices (IVDs) and their components is regulated by the Food and Drug Administration (FDA) under the Food, Drug, and Cosmetic Act (FD&C Act), as amended. Laboratory test systems that are sold by a manufacturer or developed by a laboratory are known, in regulatory parlance, as *in vitro* diagnostic devices, and fall under the purview of the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) of the Center for Devices and Radiological Health. OIVD performs its premarket review efforts through three subordinate divisions, Immunology (including hematology and pathology), Microbiology, and Chemistry. Premarket review of IVDs for infectious agents that involve the blood supply and for retroviral testing is usually performed within the Center for Biologics Evaluation and Research.

Although most members of the laboratory community are aware of the FDA role in premarket review of IVDs, the manner by which the FDA discharges its regulatory responsibilities often appears arcane or opaque to health care providers, laboratorians, and the public alike. This article attempts to provide a bird's eye view of the process by which the FDA classifies IVDs on the basis of risk, clears or approves these devices before marketing, and conducts postmarket regulation of diagnostic device performance.

Premarket Regulation

The role of the FDA in laboratory medicine is to help assure that commercially distributed laboratory test systems are safe and effective for their intended applications. Effective use of resources dictates that FDA oversight should focus on those devices that pose the greatest potential threat to patient safety. By statute and regulation, Congress and the FDA have developed a system of device classification to facilitate different levels of oversight for devices having different risk profiles.

The FD&C Act describes both the basis for classification and most of the regulatory terms. Additional information on the classification process has been codified in device regulations (21 CFR 860). As a result, classification and regulation are a well-defined process. Device classification depends on the intended use of the device and also on indications for use. Intended use defines what is tested (such as presence or absence of the factor V Leiden mutation). The indication for use describes why a patient would be tested (to determine risk of deep venous thrombosis). Classification is based on the risk the device poses to the patient or the user and the

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information available to address that risk. Class I includes devices with the lowest risk (such as immunohistochemical reagents used as adjuncts to diagnosis) and class III includes those with the greatest risk (such as digital image analysis systems for Pap smears). Class II devices typically present moderate risk to patients and users (such as molecular tests for prothrombin G20210A or factor V Leiden). The classification of a device generally determines the premarket regulatory approach that is taken by the FDA and device manufacturers. In most cases, the classification that will be applied to a new diagnostic device is fairly obvious if other tests detecting the same analyte have already been cleared or approved by the FDA. When classification of a new diagnostic device is not clear, a manufacturer may request information on how the FDA might classify a new device before a submission is made, either in a formal nonbinding process [known as a 513(g) determination] or by an informal nonbinding route (by discussion with the appropriate OIVD divisions).

Premarket Approval (PMA)

IVDs that have substantial importance for prevention of impairment of health, or that have a potential unreasonable risk of illness or injury (whether by themselves, or because of the way the test results are used for medical decision-making) and for which general and special controls are considered inadequate, are class III devices. As such, they are subject to the highest level of review—premarket approval, or PMA. In addition, devices that test for a new analyte (or substance) or claim a new intended use for an existing analyte that has not been the subject of any previous submission to the FDA, will automatically be placed into class III and may require premarket approval (see *De Novo* Review section). Some examples of class III devices are those that are intended to make a diagnosis of cancer, or identify or monitor infection with certain organisms (such as human papillomavirus, which is used together with cytological examination to detect premalignant lesions of the cervix). The PMA application typically contains a complete record of the studies performed to support a reasonable assurance of safety and effectiveness for use of the device, as well as information on how the device is designed and manufactured. A device that requires a PMA must be shown to provide a reasonable assurance of safety and effectiveness for its intended use completely on its own merits; comparison to other devices is not necessary, and is usually not sufficient.

PMA applications reflect both preclinical evaluation by the manufacturer (testing performed before the device is used in a clinical trial) and evaluation of clinical performance (usually testing performed on samples from patients who fit predefined enrollment criteria). The preclinical section generally demonstrates that the device can accurately and reproducibly measure the analyte under controlled conditions. An example would be the demonstration that a test system reproducibly identifies genetic abnormalities in patients with a clinically manifest hereditary disease, and does not report abnormalities in those

that do not have the disease. The clinical section must show that the device provides the expected result, whether positive or negative, in defined patient populations that reflect the intended use of a device.

Because clinical trials are intended to reflect the performance of a device in routine clinical practice, it is usually not sufficient for a manufacturer to demonstrate performance in its own laboratories. In general, the FDA will require that clinical trials be conducted in representative outside clinical laboratories that reflect the expected market for the test system. In certain situations, a body of recognized literature may substitute, or partially substitute, for clinical studies.

To be approved, a device should have clear clinical validity and effectiveness, ie, its use should add value to a health care provider's ability to make appropriate medical decisions. When necessary, the FDA will seek the advice of outside experts who have been appointed to the agency's Medical Device Advisory Committee to provide decision-making advice.

The application is reviewed within the FDA by a group of regulatory scientists that typically includes clinical laboratorians, medical officers, engineers, and statisticians. Frequently, the FDA will request clarification of the submission before making a final decision. FDA statisticians review both study design and provide an analysis for bias or error that may have an impact on study results. Usually FDA statisticians perform their own independent analyses of the raw data. In most cases, the clinical trials themselves are audited for compliance with good laboratory practices. Finally, manufacturers can expect to be inspected to assure their compliance with the Quality System Regulation (QSR) before they are allowed to market a new high-risk laboratory test.

The average time between receipt of an original PMA by the FDA and a final decision is ~8.5 months, based on 10 applications approved between October 2002 and March 2003, which includes both the FDA review time and time required by the manufacturer to provide additional requested information.

Premarket Notification [510(k)]

Since implementation of the Medical Device Amendments to the FD&C Act on May 28, 1976, anyone wishing to sell a medical device in the United States may be required to make a 510(k) submission at least 90 days before offering the device for sale. In addition, a 510(k) submission is required if a manufacturer or distributor proposes a different intended use for a device already in commercial distribution, or there is a change or modification of a device that could significantly affect its safety or effectiveness. However, certain class I or II devices can be marketed for the first time without having to submit a 510(k). Many analyte-specific reagents fall into this category, as do many other types of general laboratory supplies and reagents.

Devices that require 510(k)-level review can be class I or II, but most are class II (ie, have a moderate risk when the results are used for medical decision-making). Prothrombin G20210A and factor V Leiden genotyping as-

says performed on the LightCycler (Roche Diagnostics, Indianapolis, IN) both fall within this group. 510(k) submissions for IVDs usually include preclinical data and may or may not include clinical data from patient samples depending on how much is already known about the characteristics of the device/analyte combination. A device that is cleared, ie, found to be substantially equivalent, exhibits similar performance characteristics to the predicate (or previously cleared) device or reference method to which it has been compared for the same intended use. A device that is found to be not substantially equivalent usually has different performance or technological characteristics or a different intended use. When there is no predicate device to which a new device can be found substantially equivalent, a *de novo* review process may be indicated (see *De Novo Review* below). Devices that are found to be not substantially equivalent may not be marketed. The options of the submitter then include submitting a PMA, pursuing *de novo* classification, or reconsidering the device use and validation. The average time between receipt of a 510(k) by the FDA and final decision is just over 3 months, based on 354 decisions rendered between October 2002 and March 2003, including the FDA review time and time required by the sponsor to provide additional requested information.

De Novo Review [513(f)(2)]

A device that measures a new analyte or has an intended use for which no submission has previously been cleared or classified as a class I or II device is automatically assigned a class III designation, which would require a PMA submission. As a result of the FDA Modernization Act of 1997, the FDA now has increased flexibility in classification of these devices. In cases in which the FDA believes the risk of a device is sufficiently low (based on intended use or on information that allows for mitigation of risk for an intended use), the FDA may choose to use provisions of the new law to classify a new device as class I or II. In this case, the new device may be tested by the manufacturer in the same way as it would be for a PMA (eg, includes clinical studies), but is reviewed in a process similar to the 510(k) process. This decreases the administrative burden on both the manufacturer and the FDA and eliminates the requirement for premarket assessment of QSR conformance (although conformance to the QSR is still required, and may be assessed after market through either random or directed inspections). The sponsor first submits the *de novo* candidate submission as a premarket notification [510(k)]. To accommodate the classification system in place under the existing statute, as a formality, this submission is found to be not substantially equivalent. After receiving the not substantially equivalent decision, the sponsor or manufacturer then submits a request for *de novo* classification. In response, the FDA will issue an order classifying the device into class I or II, or determine that it will remain in class III. If classified into class II, a special control guidance document will usually be written and published. Additionally, if classified into class I or II, the device can then serve as

a predicate for subsequent 510(k) submissions with the same analyte and intended use.

Obviously, this is a somewhat nuanced process that is best accomplished by preliminary discussion and interaction with the FDA. OIVD has used the process 13 times since January 2003, and is able to process *de novo* classifications in time frames of less than a week when working collaboratively with sponsors. The FDA has recently approved factor V Leiden and factor II genotyping kits. Although these had no predicates and by default would have been considered class III devices and required PMAs, the FDA processed the factor V as a *de novo* 510(k) using the analytical information provided by the sponsor and the rich clinical literature cited by the sponsor to allow approval as a class II device with a special control guidance document. The factor II submission was then found substantially equivalent to the newly classified factor V test system.

Class I Exempt Devices

Class I IVD devices typically present low risk(s) to the user or patient when used to make medical decisions. Premarket submissions are not required for class I exempt devices. However, a manufacturer must submit a premarket notification for class I devices that are not exempt (see below). Exemption generally means that a premarket notification is not necessary to provide a reasonable assurance of safety and effectiveness and that the other general controls are sufficient to provide such as reasonable assurance. General controls, other than premarket notification, mean that:

- 1) the device is manufactured according to the QSR;
- 2) the device is labeled according to requirements in 21 CFR 801 and 809;
- 3) the manufacturing establishment is registered and the device is listed with the FDA;
- 4) the device is subject to being banned if found to present substantial deception or an unreasonable and substantial risk of illness or injury;
- 5) in certain circumstances, the manufacturer must notify the purchaser if any changes are made to the device;
- 6) the manufacturer is required to keep certain records; and
- 7) other general requirements may apply.

Class I Reserved Devices

"Reserved" means that a class I device is not exempt from premarket notification. Class I reserved devices need premarket notification [510(k)] to provide a reasonable assurance of safety and effectiveness. These devices may be intended for a use of substantial importance in preventing impairment of human health or present a potential unreasonable risk of injury or illness.

Investigational Device Exemption (IDE)

Sometimes the proper validation of a laboratory device requires not only that results be validated on clinical

samples, but also that these studies be conducted in a manner that affects clinical care. Without premarket review or approval, however, a device cannot normally be distributed for patient care purposes because it has uncertain potential for illness or injury to patients. The IDE provides a mechanism by which the safety and effectiveness of medical devices can be evaluated during clinical trials. Two types of IDE exist. For nonsignificant risk devices, review of the protocol and study requirements fall under the purview of the local institutional review board and no submission to the FDA is required. For significant risk devices the manufacturer presents the FDA with a proposal for evaluating the device. The proposed studies must be approved by not only the FDA, but also by the appropriate institutional review board. Assuming the reviews show that the risks are adequately disclosed to patients and that the benefits of the study are sufficient to offset these risks, the IDE is generally granted. The IDE allows distribution and investigation of the device to determine the performance characteristics in the clinical setting. The FDA expects that institutional review boards will diligently perform their roles as oversight groups, and may inspect them to assure compliance with the human subjects regulations in 21 CFR parts 50 and 56; the studies may also be subject to 45 CFR part 46.

Most investigations of IVDs do not require an IDE. An example of an investigation that would require an IDE is a study in which the diagnostic test will be used to select certain patients with serious conditions for treatment, and exclude others. Some devices used in the diagnosis of cancer or certain heritable diseases fall in this category.

Laboratory-Developed Assays

Laboratory-developed assays are those that are assembled, validated, and performed within a clinical laboratory, and the results of which are provided for clinical care. The assays are not sold to other users. Laboratory-developed assays may incorporate analyte-specific reagents (ASRs) sold by manufacturers or they may use reagents produced entirely by the laboratory. Laboratories that make and perform laboratory-developed tests (with or without using ASRs) are not required to submit data on the test for FDA review. Instead, laboratories that develop their own clinical diagnostic tests must follow the regulations of the Clinical Laboratory Improvement Amendments of 1988.

Analyte-Specific Reagents

ASRs are considered active ingredients used in diagnostic tests for identification and/or quantification of a chemical substance, ligand, or biological target in patient specimens. An ASR is generally a single reagent, such as an antibody or nucleic acid probe, that can be used by laboratories in developing a functional clinical assay. Companies that sell ASRs must register their establishments and list their reagent(s) with the FDA. They are expected to manufacture ASRs according to the Quality Systems Regulation (QSR). Manufacturers can provide

information about the reagent to the user such as identity and purity, but should not provide information on specific performance characteristics (such as sensitivity or specificity) or claims. Instead, the user assembles the clinical assay using the ASR, and then is required to validate the performance of the new assay in the intended population.

Although most ASRs are considered to be class I devices and thus exempt from premarket approval or notification requirements, the rule does provide for some exceptions. Reagents used to test for analytes used in blood banking tests that have been classified as class II devices (eg, certain cytomegalovirus serological and *Treponema pallidum* test reagents) are considered class II ASRs. Reagents used to test for analytes intended for use in donor screening or "for the diagnosis of a contagious condition that is highly likely to result in a fatal outcome, and prompt, accurate diagnosis offers the opportunity to mitigate the public health impact of the condition" are considered class III ASRs. The "ASR rule" is not intended to be a mechanism by which manufacturers can avoid premarket review by simply labeling a reagent or test system as an ASR, particularly because class II and III ASRs require premarket notification or approval before marketing.

General Purpose Reagents (GPRs)

General purpose reagents are those that have general laboratory application and are not labeled or intended for specific diagnostic applications. Laboratory machinery and automated or powered systems are not considered to be GPRs. Some examples of GPRs are certain buffer solutions, some enzymes, and so forth, that could be used in the development of many different types of test, and are not analyte specific. GPRs are exempt from premarket notification [510(k)] when used in laboratory-developed tests. GPRs are also exempt from certain parts of the QSR, if they are not represented as sterile.

Research Use Only Devices

Although most researchers do not make a distinction between research and investigation work, the FDA does distinguish between these two terms. Research use only devices (RUOs) are intended for performing basic scientific or animal research in the search for a diagnostic hypothesis or intended use for a new diagnostic device. These are not considered effective IVDs and labeling should bear the statement "For Research Use Only. Not for use in diagnostic procedures." RUOs require no premarket regulation except for this labeling requirement. These devices are not subject to good manufacturing practices or other general controls. RUOs are not intended for use as building blocks for laboratory-developed assays and this category of products is not intended to be used to facilitate the reporting of results to patients or health care professionals for clinical purposes. Examples of RUOs would be devices used in basic science research (ie, to investigate a newly discovered inflammatory pathway or for use in looking for new markers associated with a particular tumor or other disease).

Investigational Use Only

Most *in vitro* diagnostics that are undergoing initial development and evaluation are exempt from IDE submission, but are considered investigational use only (IUO) devices while clinical studies are being performed. The minimal requirements for IUO devices exempt from IDE are that the testing is noninvasive, does not require invasive sampling presenting significant risk (routine phlebotomy is acceptable), does not introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic device or procedure. IUOs are intended to be used to gather data to support an intended use for a device that will be the subject of premarket review. IUOs must be labeled: "For Investigational Use Only. The performance characteristics of this product have not been established." IVDs labeled "Investigational Use Only (IUO)" are not intended to be used for obtaining test results from human specimens for the diagnosis, treatment, or management of patients without confirmation by other medically established procedures. Institutional review board review (21 CFR Part 56) and informed consent (21 CFR Part 50) apply. Virtually all submissions to OIVD (from basic analytes such as sodium and hemoglobin to complex new genomics tests or novel tumor markers) are studied as investigational use devices with or without the use of the IDE process.

Controls

For the FDA's regulation of IVDs, the term "controls" can have either of two meanings. One is the meaning usually assigned within the laboratory as reagents or systems that are used to assure that a test system is functioning properly. In a regulatory context, however, controls may also refer to a set of requirements or guidances that are in place and intended to help assure that a device performs in a safe and effective manner in actual use. In this sense, there are two types of controls, general and special, on which the FDA relies.

General Controls

General controls are minimum requirements for assurance of safety and effectiveness of a device. They include:

1. Establishment registration of companies that are required to register under 21 CFR Part 807.20, such as manufacturers, distributors, repackages, and relabelers.
2. Medical device listing with the FDA of devices to be commercially distributed.
3. Manufacturing devices in accordance with Good Manufacturing Practices in 21 CFR Part 820.
4. Labeling devices in accordance with labeling regulations in 21 CFR Part 801 or 809.
5. Submission of a premarket notification [510(k)] before marketing a device.

Special Controls

Special controls are measures that are put in place for class II devices for which general controls alone are insufficient to provide a reasonable assurance of safety and effectiveness. All class II devices require special controls. Special controls are existing methods that are enumerated by the sponsor and the FDA to provide assurance of safety and effectiveness, including guidance documents, with performance specifications and labeling recommendations, mandatory performance standards and postmarket surveillance. The use of general and special controls is not considered sufficient to assure safety and effectiveness of class III devices, for which a more complete demonstration of safety and efficacy is provided through the PMA process.

The FDA Role in Facilitating the Introduction of New Diagnostic Devices

The FDA clearly understands that in its efforts to promote public health, new devices that have a significant and positive public health impact should be made available as quickly as possible. The FDA uses two processes, the pre-IDE and expedited review, to make this possible.

Pre-IDE

One way to speed the approval of new diagnostic devices is to engage the FDA actively before submitting devices for premarket clearance or approval. The pre-IDE process by which this occurs begins when a sponsor submits a proposal or protocol to the FDA, to seek advice on likely regulatory requirements. In lay terms, this can be viewed as a free FDA consulting service. Despite its name, a pre-IDE for an IVD does not usually lead to an IDE submission, but rather to an informal and nonbinding agreement on the approach by which to develop a 510(k) or PMA submission. The FDA review staff carefully reviews these submissions, which describe plans for analytical, clinical, and statistical studies. The results of this review are then communicated by phone, letter, e-mail, or personal meeting. Working together, the FDA and sponsor can arrive at a mutual understanding of the scientific, medical, and regulatory issues raised by the submission, so that they can be addressed adequately before clinical investigations begin. This process is especially helpful when a device will test a new analyte or intended use, or has other unusual properties for which the sponsor would like the FDA's perspective. Agency agreement on a pre-IDE protocol does not imply that a submission following that protocol will be acceptable, but only that the types of studies and intended uses proposed are considered acceptable for gathering and analyzing the required data. When a pre-IDE process occurs, however, the regulatory staff often finds the final formal submissions to be more complete, easier to review, and to raise fewer issues that hinder clearance or approval.

Expedited Review

FDA review of an application [either PMA or 510(k)] may be expedited either on request of the sponsor of a new device or based on the FDA preliminary review. To merit expedited review, the condition to be diagnosed must be life-threatening or irreversibly debilitating, and the device address an unmet medical need, as demonstrated by any one of the following: breakthrough technology, no approved alternative, significant clinically meaningful advantage, or, in the best interest of patients. Expedited review means that the submission moves to the head of the review queue, and that additional resources may be applied to accelerate the review process. Although this assures that the FDA makes review of the device of interest a high priority, it does not guarantee a particular review outcome or time line. The single most important criteria determinant of review time is the quality of the submission. Sponsors with devices that could be eligible for expedited review are encouraged to work with the FDA in the pre-IDE process to ensure that review questions have been addressed and criteria have been met. It is strongly recommended that companies use all requisite scientific, statistical, and regulatory resources appropriate to ensure that submissions are clear, complete, and can be reviewed quickly.

Standardization of Premarket Review Processes

The FDA has worked hard to develop a standardized review process that is based on state of the art evaluation techniques and is grounded in the Food and Drug Administration Modernization Act of 1997 (FDAMA) mandate to provide least burdensome premarket reviews. The FDA has considerable resources to draw on in helping companies establish performance of new IVDs, including growing literature devoted to test performance, a total of 73 recognized standards, and multiple review guidances. Recently the new OIVD has developed a generic summary data template for final review memos. Links to summaries of cleared or approved products can be found on the OIVD web site (<http://www.fda.gov/cdrh/oivd/>). These summaries provide insight into the review process for a wide variety of products.

Postmarket Review Tools

The QSR

Perhaps the most important new regulatory tool developed by the FDA during the past 10 years is development of revised regulations for good manufacturing practices. This revised regulation, termed the "quality system regulation" (QSR) has been codified in 21 CFR 820. They were developed in harmony with international standards for

quality systems and include a variety of quality based production requirements. For selected class I, and all class II and class III devices, the QSR calls for the implementation of design controls. These dictate that the manufacturer of a product identify both device inputs and outputs, ensure verification of performance, and establish validation of performance to predict and ensure proper use in the hands of the intended user. By emphasizing the need to build quality into the design of product and by introducing a variety of process and production controls and corrective action requirements, the FDA has introduced a paradigm for ensuring quality production of medical devices.

Postmarket Reporting of Adverse Events

Postmarket control of medical devices is further monitored by existing requirements for reporting problems to the FDA and for companies to take corrective action when problems are identified. Throughout the past decade, the FDA has developed a new reporting system, MedWatch (<http://www.fda.gov/medwatch/>) to make reporting of medical product problems to the FDA more user friendly. Standardized forms have been developed and are available by phone, fax, or internet. For IVDs, monitoring of MedWatch reports is now performed by more than a half dozen technical analysts who also participate in premarket review and compliance actions. Most recently, OIVD has launched a pilot based on the active surveillance program (the MedSun program) being developed by the Office of Surveillance and Biometrics. This LabSun pilot was evaluated at several laboratories and now is being expanded to include all MedSun facilities with laboratories. It is hoped that this will lead not only to better postmarket regulatory oversight, but more sophisticated outreach and educational initiatives and more informed premarket decision making.

Summary

The FDA regulatory program for IVDs is a complex and nuanced initiative that attempts to consider IVD performance at all phases of the device life cycle. This article defines the classifications, process, and regulatory terminology in more clear terms in a cohesive format. The definitions and terms listed here do not replace or modify any existing regulations or regulatory language. They are provided as an aid to understanding some of the more complex regulatory concepts that are frequently encountered in developing and understanding device submissions. These definitions concern generalities only and may not apply to any specific device or situation. One should always consult a regulatory specialist or the FDA for specifics regarding any device intended for marketing or for which you seek regulatory information.