

3. Regulatory Pathways for Clearance or Approval of IVDs

By Jeffrey Gibbs*

I. Introduction

In vitro diagnostics (IVDs) are playing an increasingly important role in the practice of medicine. The goal of personalizing medicine has been widely recognized as critical to improving outcomes. Without better diagnostic tools, this goal is unattainable. Spurred both by the need for novel diagnostics and the proliferation of new technologies, there has been an explosion in new tests for measuring analytes, new biomarkers and new diagnostic intended uses.

From a scientific perspective, this may be a “Golden Age” of diagnostics. The sequencing of the human genome, the development of methods for identifying and quantifying minute amounts of biomarkers, and new computational techniques that allow the development of algorithms that define relationships between biomarkers and clinical conditions have combined to stimulate the development of thousands of new tests.¹ This has been facilitated by new instruments that make analyses faster, cheaper and easier. The new IVDs are expected to play an important part in changing the way healthcare is provided with “recent major advances in science and technology, such as those associated with molecular-level and genetic testing... leading to changes in clinical practice.”²

The development of an assay, though, does not mean that it ever will be commercialized. Many obstacles need to be surmounted, including regulatory ones. The gatekeeper for the market entry of IVDs in the United States is the Food and Drug Administration (FDA). This chapter will summarize some of the key elements of the FDA regulatory system for IVDs.

One of the threshold decisions for an IVD developer—particularly for the most novel assays—is whether to seek clearance or approval from FDA, or to market the assay as a laboratory developed test (LDT). From the enactment of the Medical Device Amendments of 1976 until the past few years, these were two entirely separate and discrete categories. This formerly fine line has become blurred. FDA has now asserted a larger role over laboratories and some LDTs have undergone FDA premarket review and clearance. Thus, laboratories are now being regulated by FDA. Concurrently, some IVD kit manufacturers have acquired or established laboratories. Many aspects of FDA regulation over LDTs are unclear. However, it seems likely that the role played by FDA in regulating laboratories will grow.

LDTs are discussed at length in Chapter 6 of this book. Accordingly, this chapter focuses on IVDs that are developed and submitted to FDA for commercialization as a test kit.

Nevertheless, this chapter is relevant both to manufacturers who seek to market IVDs, as well as to laboratories that either will elect to submit a marketing application to FDA or will find themselves being regulated by FDA.³ This chapter addresses some of the key aspects of marketing IVDs, including the regulatory review processes, intended use, data requirements and the Quality System Regulation (QSR).

II. Routes to the Market

The universe of IVDs is quite diverse. Some diagnostic tests have been around for decades and are well-established clinically. Other assays are novel. Similarly, some instruments used in diagnostic tests have been available—at least in some form—for decades, while others are brand new. The range of assays is equally heterogeneous, from single markers for basic blood chemistry (e.g., triglycerides and cholesterol) and influenza A, to new strains of influenza (H1N1) to complex assays, e.g., multi-protein, algorithm-derived tests for detecting cancer.

This diversity provides a challenge when describing the FDA review process. The route to market for a home glucose test is entirely different for a multi-marker, algorithm-based assay that is an adjunct to detecting the presence of lung cancer. The basic regulatory requirements are formalistically the same, and yet the two applications for those two tests would share little in common. This chapter covers the basic principles applicable to all IVD applications,⁴ while focusing more on the newer tests, since they provide the more difficult regulatory road than do the better-established IVDs.⁵

There are two primary routes to the marketplace for new IVD assays and instruments⁶: pre-market notifications (commonly referred to as 510(k)s) and premarket approval applications (PMAs). The overwhelming majority of new IVD assays enter the market through the 510(k) process. For example, in 2005, the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) cleared 434 510(k)s and approved nine PMAs.⁷

III. The 510(k) Premarket Notification Process

A. Selecting a Predicate Device

In order to obtain 510(k) clearance, a company must show that its device is “substantially equivalent” to a “predicate device.” These basic requirements are no different for IVDs than for any other device regulated by FDA. Nor do those requirements vary based on the type of

IVD. However, the way in which these requirements are applied can be markedly different for IVDs than for other categories of devices, and also diverge widely within the universe of IVDs.

A “predicate device” may be either a device which was on the market prior to May 28, 1976, or one which has subsequently been cleared by FDA. There will be few, if any predicates, that fall into the former category. Thus, when searching for predicate devices, companies should focus on products that have obtained 510(k) clearance. It is not necessary that the product be currently marketed; a product can serve as a predicate device if it is 510(k)-cleared even though it is no longer being sold.

A 510(k)-cleared IVD can also serve as a predicate device even though it incorporates a different technology. Given the dramatic technological shifts in diagnostics, this is an important principle. A company with, for example, a polymerase chain reaction (PCR) assay could use a monoclonal antibody-based assay as a predicate, if the proposed intended use is at least roughly the same as the predicate’s intended use. Hence, when searching for a predicate (or predicates, since a 510(k) can cite more than one predicate device), the applicant should focus on similarity of intended use, not just technological similarities. A company can generate data to show that its product performs equivalently to an assay incorporating a different technology.⁸ Bridging a large gap between the new intended use and the cleared intended use can be far more problematic.

The Federal Food, Drug, and Cosmetic Act (FDCA) states that the new device must “ha[ve] the *same* intended use as the predicate device.”⁹ If followed literally, that could mean the intended uses of products would have essentially been frozen in time, permitting no advances in diagnostic claims through the 510(k) process. Fortunately, the Center for Devices and Radiological Health (CDRH), including OIVD,¹⁰ has not rigidly interpreted this language. While the IVD applicant must identify a predicate device whose intended use is directly relevant to the new proposed intended use, some flexibility has been exercised. For example, OIVD has cleared assays for Lyme Disease, even though no predicate device had referenced the disease in its intended use statement before this disease emerged, and for a tissue of origin test for malignant tumors, which cited a rather different medical decision software product as a predicate.

One of the recurring issues for OIVD has been whether a 510(k) applicant can use a laboratory method as the predicate device. Laboratory tests, such as culturing an infectious agent, have often been the “gold standard” against which an IVD’s performance was judged.

Historically, there have been occasions where applicants cited culture. For example, as new diseases appeared, there could not be a 510(k)-cleared assay for that same etiological agent, and applicants cited the laboratory method—which was being used to identify the disease—as the predicate device. Whether that approach will always be permitted in the future is uncertain, given that a laboratory method can establish the validity of the assay, but has not itself been cleared. However, in view of the flexibility of the 510(k) process, there should continue to be mechanisms by which these assays can be introduced through the 510(k) process.

Companies faced with this situation would, however, be well-advised to consult with OIVD at an early stage regarding their regulatory strategy if the lack of a predicate device may present an obstacle to obtaining 510(k) clearance.¹¹ One thing that is clear, though, is that a product labeled as “Research Use Only” (RUO) cannot serve as a predicate device.¹²

Whether a product can be reviewed through a 510(k) rather than a PMA will often hinge not on whether the same analyte already has been cleared via a 510(k), but on the specific intended use. For example, a prostate-specific antigen (PSA) assay can be cleared through a 510(k) when intended for monitoring a patient with prostate cancer. The identical assay would need a PMA if the proposed intended use were to screen for prostate cancer. One recurring question companies ask is whether a particular analyte can be cleared through a 510(k). Phrased that way, the question often cannot be answered: while many analytes are presumptively eligible for 510(k) clearance, the specific intended use can change the product’s regulatory classification.

For a more novel product, it is important to find a reasonably parallel predicate device. Ultimately, though, the availability of 510(k) review for this type of product will be affected at least as much by the perceived risk as by how closely the proposed intended use matches the predicate’s. OIVD appears willing to exercise more flexibility in accepting an “analogous” predicate device if the risk is relatively low.

The level of perceived risk can be affected by the exact proposed wording of the intended use: “diagnose,” “monitor,” “adjunct,” “screen” and “risk stratification” present different levels of clinical risk. That is, whether the device is Class I, II or III¹³ can be a function not only of the biomarker being detected and the associated disease state, but also the precise clinical application. An assay that *monitors* the status of a disease by quantifying the marker’s level in a patient who has already been diagnosed with and treated for the disease presents a lower risk than an assay testing for the same marker associated with the same disease but intended to *screen* patients for the presence or absence of that disease.

Thus, the first step for an applicant is to determine whether its device is eligible for the 510(k) process. For me-too IVDs, such as glucose or troponin, the answer is “yes,” barring some novel claim. For other, newer products with a less clear-cut predicate device, the applicant should assess whether its potential intended use is sufficiently low risk to be an appropriate candidate for 510(k) clearance. With the advent of many new diagnostic tests, determining whether an IVD can proceed via a 510(k) becomes increasingly challenging, as predicate intended uses are positioned as “analogous,” rather than being the same.

This task of selecting a predicate acceptable to FDA may become more complicated. CDRH has recently received criticism from many quarters for the manner in which it has implemented the 510(k) process. As a result, CDRH has asked the Institute of Medicine to review the 510(k) system.¹⁴ It is unclear how these criticisms will affect the 510(k) process generally, or the impact on IVD 510(k)s specifically. In addition, CDRH has informally indicated that it may no longer follow 510(k) precedents that it considers to be erroneous.¹⁵ Whether this could be done lawfully is unclear, but the possibility that previously cleared 510(k)s could no longer be relied upon introduces another potentially troubling layer of unpredictability to an already complex process.

B. Demonstrating Substantial Equivalence

Demonstrating that an IVD is eligible for 510(k) review by identifying a predicate device is necessary but not sufficient. The applicant must also show that its assay is substantially equivalent to the predicate device. Proving substantial equivalence will require the submission of data. This is one way in which IVD submissions differ from 510(k)s for many other types of devices—some performance data will routinely need to be submitted.

The FDCA defines “substantial equivalence” in terms of:

with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device—

- (i) has the same technological characteristics as the predicate device, or
- (ii) —
 - (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary...., and

(II) does not raise different questions of safety and effectiveness than the predicate device.¹⁶

For OIVD, there will be a wide variety of ways for meeting that standard.

It is impossible to generalize as to the type or quantity of data that will suffice to show substantial equivalence. At one end of the spectrum, a company may need to submit a relatively limited amount of comparative evidence demonstrating that its IVD performs the same as the predicate device, e.g., testing a relatively small number of samples with both products and showing the degree of concordance. The application also may need to be supported by other, noncomparative analytical studies, such as limit of detection, within-laboratory precision/repeatability, interference and cross-reactivity.¹⁷ At the other end of the spectrum, the applicant may need to conduct a prospective multi-center clinical trial with clinically established endpoints serving as diagnostic “truth,” i.e., the ultimate determinant of accuracy.

One of the many issues that must be considered is the endpoint of the study. Is the goal to show concordance with an already cleared assay? This can be a relatively simple study to perform, but the claims are necessarily limited, because it is unknown where “truth” lies in the discrepant samples. Other 510(k)s will attempt to resolve “truth” by using some other method or by comparing assay results to a “gold standard,” e.g., clinical diagnosis.¹⁸ This may enable the company to claim sensitivity (the ability to accurately detect the disease) and specificity (the ability to avoid false positives). Other kinds of claims are also possible, such as negative predictive value and positive predictive value.¹⁹

Another aspect that deserves careful consideration involves statistical analysis. There can be many different ways of analyzing the same data. In some instances, the statistical plan can be simple and straightforward; in other instances, the statistics can be remarkably complex. In addition, OIVD is requiring a greater degree of statistical rigor than it once did. Before initiating a clinical study, the company should consider how it will statistically analyze the data; this forethought is particularly important for more novel tests.²⁰ Companies should seek biostatistical input before embarking on costly studies to support 510(k) clearance (or PMA approval).

C. Developing and Submitting Data

Applicants have multiple resources upon which to draw in assisting them to determine what data need to be generated and submitted. After a 510(k) is cleared, FDA will post the applicant’s own summary of safety and effectiveness on the FDA website. While often not very

detailed, this document can offer some insights into the kinds of data that were submitted.²¹ In addition, OIVD will often make available copies of its decision memorandum.²² These internal documents furnish helpful insights into what data were submitted and how OIVD reviewed those submissions.²³

510(k)s are also available through Freedom of Information Act (FOIA) requests.²⁴ However, because FDA typically takes several years to process FOIA requests, this mechanism is often of limited utility. Furthermore, the 510(k) applicant has the opportunity to redact the document, further reducing the insights it will offer. An applicant may find, though, that a 510(k) of interest had already been released in response to a prior FOIA request; this can result in much faster access to the submission.

OIVD's guidance documents represent a key class of documents that must be considered. There is a general guidance document on 510(k)s, entitled "In Vitro Diagnostic Devices: Guidance for the Preparation of 510(k) Submissions."²⁵ OIVD has also generated dozens of guidance documents for submissions of specific tests ranging from "Anti-Nuclear Antibody Test Systems"²⁶ to "Coagulation Instruments."²⁷ As guidance documents, these statements are not legally binding.²⁸ Nevertheless, an applicant should carefully evaluate what a guidance document says in developing its submission strategy and writing its 510(k).

OIVD also periodically releases draft guidance documents.²⁹ Even though a draft guidance document that applies to a particular type of assay is not a definitive statement of law or even agency policy, an applicant should carefully assess its contents. While OIVD could not correctly state that this draft guidance establishes legal requirements, draft guidance documents may embody the reviewers' expectations of the data they believe ought to be in a 510(k). Moreover, a draft guidance may be adopted in final form between the time the would-be applicant goes from developing its regulatory strategy to when it completes the 510(k) process.

Companies contemplating the submission of a 510(k) should also be alert to other sources of information that might affect their 510(k)s. Awareness that a new or modified regulatory approach may be put in place by OIVD can come from a variety of sources, such as speeches by OIVD officials, statements by major medical organizations (American Society of Clinical Oncology, American College of Obstetrics and Gynecology (ACOG), etc.) about the disease being detected by the assay, and publications in major medical journals regarding the disease or existing diagnostic tools. For instance, a position paper issued by ACOG concerning the clinical value of a biomarker on the standard of care for managing a condition diagnosed by that biomarker may trigger a tightening by FDA of its own data requirements.

While 510(k) applicants should obtain and assess these various sources of information, they should not assume that the past is automatically prologue. The data that were acceptable for a 510(k) cleared five years ago may not be acceptable any longer. A good illustration of the evolving expectations for 510(k)s comes from OIVD's guidance document entitled "Class II Special Controls Guidance Document: Testing for Detection and Differentiation of Influenza A Virus Subtypes Using Multiplex Assays." Issued in 2009, this guidance document sets out OIVD's expectations for assays for the detection and identification of Influenza A viruses. Of course, OIVD cleared multiple influenza assays prior to the release of this guidance document. An applicant who used as its model a 510(k) that significantly pre-dated this guidance document, though, might find that OIVD would not consider the data to be sufficient to establish substantial equivalence. This could be the case even if the company were using its own previously cleared assay as the predicate and submitted the same data set that had been successful before.³⁰

An IVD company should not automatically assume that the data sufficient even a few years ago for a 510(k) will now be adequate for a new version of the same assay. More changes may be in the offing. The current Director of OIVD was quoted as saying that substantial equivalence is "not anchored very well" and, "you get, essentially, tests that are all over the place."³¹

IVD companies are reporting—with some surprise and concern—that the same data sets that sufficed a few years ago are not now considered acceptable for closely related assays. The modification by OIVD of data requirements without public notice does present some significant difficulties for industry.³²

Once the 510(k) is submitted, OIVD may take one of several actions. OIVD may determine that the product is substantially equivalent to a valid predicate device and clear the 510(k).³³ This action permits the device to be marketed. A second option is to issue an Additional Information (AI) letter. The applicant then has the opportunity to respond to the questions. These questions may range from the relatively simple, e.g., revision of labeling or revised analysis of existing data, to the much more challenging, e.g., redoing analytical studies or generating supplemental clinical information. In some cases, the applicant will respond successfully to the AI letter; sometimes the applicant is not so fortunate.

If OIVD decides that the assay is not substantially equivalent (NSE), it will issue a letter to the applicant apprising the company of that determination and the grounds. Most often, the

NSE is based on a finding that the product has not provided sufficient information to demonstrate substantial equivalence. Upon receiving the letter, the applicant can either appeal³⁴ or try to generate the data necessary to address OIVD's concerns and submit a new application, which may be a 510(k) or a PMA.

In some instances, however, OIVD will find the product NSE simply for lack of a predicate device. In that setting, the applicant may be able to avoid submitting a PMA through the *de novo* classification process.

D. De Novo Classification

When Congress enacted the Medical Device Amendments (MDA) of 1976, it required 510(k) applicants to identify a predicate device. If a suitable predicate device could not be identified, the product was automatically placed into Class III—and therefore required a PMA. This was the outcome regardless of the product's level of risk.

Mandating PMA review for low or moderate risk devices due to the absence of a predicate made little policy sense and was inconsistent with the risk-based framework of the MDA. Congress attempted to rectify this problem in 1997 when it passed the FDA Modernization Act. That law gave FDA the authority to automatically reclassify—or go through “*de novo* classification”—510(k)s for which there was no predicate device when the device is low or moderate risk.³⁵

Under the *de novo* process, the applicant submits a traditional 510(k). If OIVD concludes that the product is a suitable candidate for automatic reclassification, the NSE letter will essentially invite the applicant to submit a request for *de novo* classification. Thus, in this instance the receipt of the NSE letter is desirable—it allows the applicant to proceed to the next stage.

After receiving the NSE letter, the applicant has 30 days in which to submit a request for *de novo* classification.³⁶ The letter seeking *de novo* classification can be a form letter; OIVD can even supply to the applicant a copy of the standard template.

Once OIVD receives the request for *de novo* classification, it has 60 days in which to act.³⁷ Barring some very unusual circumstances, the denouement for a company whose NSE letter invited the submission of a *de novo* classification request should be the granting of the request and the clearing of the 510(k).

The likelihood of success, however, is much lower if the applicant received a conventional NSE letter citing the lack of a predicate. While nothing prevents a company in this posture from submitting a *de novo* request, the odds are against prevailing.

It is possible for OIVD to determine on its own initiative that an IVD should proceed through the *de novo* process and invite the company to consider a *de novo* submission. Companies, though, should be prepared to raise the issue with OIVD. Applicants often realize when developing their regulatory strategy that a plausible predicate may not exist, and *de novo* presents the best alternative. Companies considering the use of this mechanism, however, would be well-advised to raise the issue at an earlier stage with OIVD. For a company with a novel, moderate risk IVD for which there is no clear predicate device, it may want to broach the topic of *de novo* status to OIVD long before submission of the 510(k). There is no assurance that OIVD will decide at that point whether *de novo* is viable.³⁸ Sometimes, OIVD will take the position that it first needs to see the data. Even if no firm commitment from OIVD can be obtained, having this discussion can be valuable.

As part of the *de novo* classification process, following clearance of the device, OIVD will issue a special controls guidance document. The guidance document lays out the information that should be contained in future 510(k)s for products in this classification, and therefore helps subsequent applicants.³⁹

Thus far, *de novo* has been used relatively sparingly. Through the end of 2009, only 52 devices were listed as having been cleared through the *de novo* pathway.⁴⁰ Of those, 26 are IVDs.

IV. Premarket Approval Application

OIVD does receive, review, and approve PMAs. As noted earlier, PMAs do represent a distinct minority of applications. While PMAs are infrequent, they represent some very clinically significant diagnostics. These include tests for human papillomavirus, PSAs for screening for prostate cancer, and assays for HER/2-neu, a companion diagnostic for a breast cancer drug.

The rate of PMA submissions may increase as a result of the development of more assays intended to be used to help determine whether a particular drug should be administered to a patient, particularly oncology drugs.⁴¹ The prototypical example is the HER/2-neu test. These assays are intended as an “aid in the assessment of patients for whom Herceptin™ (trastuzumab) treatment is being considered.”⁴² Essentially, this test result will help determine whether a breast cancer patient receives Herceptin. Other companion diagnostics that have a similar intended use in determining whether a patient receives a particular oncology

agent probably will also go through the PMA process.⁴³ These PMA companion diagnostics do present some additional regulatory issues, e.g., coordination of review of the drug by the Center for Drug Evaluation and Research and the companion diagnostic by OIVD. At this point, FDA has not issued a final guidance regarding the procedures for reviewing these companion diagnostics.

To obtain PMA approval, an IVD company must demonstrate reasonable assurance of the safety and effectiveness of the device when used as labeled.⁴⁴ This will require conducting a clinical study, although a prospective study is not always necessary. In some cases, a retrospective analysis of banked specimens which were gathered for other purposes may be sufficient to generate sufficient data for PMA approval. The applicant must ensure, though, that the specimens were collected from patients whose clinical condition tracks the proposed intended use, that the necessary ancillary clinical data are available and the study can be audited. This can make it challenging to obtain PMA approval with anonymized banked specimens.⁴⁵

PMAs for novel analytes or novel intended uses are very likely to be presented to an advisory panel for review and recommendations.⁴⁶ While panel recommendations are not legally binding upon FDA, these recommendations—and the discussions themselves—will have a significant impact on the review process. Thus, it is important for the PMA applicant to prepare intensively for the panel meeting, including the submission of briefing materials and a presentation at the panel meeting itself. Other companies with the same or similar products under development should attend the meeting or obtain a copy of the transcript; these meetings can provide important insights into clinical, regulatory and scientific issues.⁴⁷

A PMA requires a major investment by an IVD applicant. For novel analytes or intended uses, a potential PMA applicant would be well advised to seek a pre-Investigational Device Exemption (IDE) meeting.⁴⁸ Even if several other PMAs have been approved for that analyte for that intended use, seeking a pre-IDE meeting may be prudent, particularly if the approvals are older. Studies that may have sufficed a few years ago may not always be deemed sufficient today. This seems especially likely in view of recent statements indicating that FDA will examine—and probably tighten—data requirements for PMAs.⁴⁹

Once a PMA has been approved, the PMA holder may want to modify the device, its labeling or the manufacturing process. FDA will need to be notified of the change; in some instances prior approval is required.

The PMA regulations give limited guidance as to what type of submission or notification is needed.⁵⁰ Recognizing the confusion in this area, CDRH has issued a guidance document.⁵¹ This document provides examples for each of the mechanisms for handling change, such as an annual report, changes being effected and PMA supplement. Although ambiguous situations remain, and this guidance document is not legally binding, IVD PMA holders can use this document to try to understand better FDA's view of what category a change falls into.

V. Other Issues in the Development of IVDs

A. Clinical Utility

Under the FDCA, it is clear that a 510(k) premarket notification and a PMA must propose an intended use. The FDCA does not expressly say, however, that the applicant must show that the proposed intended use has “clinical utility.” Could an IVD company submit an application which contains an intended use, such as the detection of a biomarker, but does not provide any evidence that this intended use provides information of clinical value?

According to FDA, the answer is no. While the phrase “clinical utility” is not expressly used in the FDCA or implementing regulations, FDA has concluded that an application cannot be cleared or approved if there is no showing of clinical utility.

This issue was most directly presented when a group of companies submitted a petition requesting the creation of a class of diagnostic termed “*In Vitro* Analytical Tests.”⁵² The basic concept was simple: these would be products where the applicant demonstrated that the biomarkers of interest could be reliably identified. Simply put, the applicant needed to show that its product could accurately measure the biomarker, but would not have to prove the clinical significance of the test result. As a corollary, the applicant could promote the IVD only for the ability to detect the analyte, and not for the clinical value of that detection. Although FDA apparently never responded formally to the petition, it did indicate strong opposition to the proposal, in part because of its view that clinical utility needed to be demonstrated.⁵³

This rejection of the petition does not mean every applicant must submit data demonstrating that its assay has clinical utility. In most cases, the clinical utility will be apparent from the identity of the marker itself. For example, the clinical value of measuring high-density lipoproteins or the presence of H1N1 does not have to be established independently by the applicant. For other biomarkers, the clinical utility can be established through published literature; the applicant can cite the research done by others as documenting the clinical utility of identifying or measuring the biomarker.

In other instances, however, neither medical practice nor the literature will establish the clinical utility. Companies that are developing assays where the assay result has no established clinical utility should carefully consider this issue and may want to obtain OIVD feedback as they develop their regulatory strategy.

Demonstrating clinical utility generally should not, however, mean the applicant must prove that better clinical outcomes ensue. Establishing that the assay reliably generates data that can assist physicians is one thing, but establishing better clinical results due to the IVD can be vastly more difficult. Many other factors having nothing to do with test performance can heavily influence patient management and the clinical outcome. For example, while PSA assays have been sold for decades, there is still controversy regarding how the results of PSA tests should be used and the extent to which PSA screening actually contributes to survival. Large-scale, well-controlled accurate studies have still not yielded a consensus on the appropriate means for managing patients with elevated PSA levels or diagnosed with prostate cancer. In this context, no IVD company should be expected to conduct studies proving that the detection of increased PSA results in lower morbidity or mortality.

B. The Pre-IDE Process

Many IVD 510(k) submissions are fairly routine. When multiple 510(k)s for that assay or instrument have already been cleared, the expected contents of the 510(k) are fairly well understood, barring changed circumstances. In other instances, OIVD has issued a guidance document that describes in some detail what information a 510(k) should contain.⁵⁴ In these kinds of circumstances, there would typically be little value in seeking to meet with OIVD prior to initiating the studies that will support the marketing application.

On the other hand, many potential 510(k) notifications and PMA applications involve some element of novelty, e.g., a new technology or a new intended use. In these settings, having a meeting with OIVD to discuss the planned submission in advance can be beneficial. This feedback can be obtained through the “pre-IDE” process.

The terminology is something of a misnomer, since only a handful of IDE applications are submitted to OIVD each year. The term “pre-IDE” is best thought of as the administrative nomenclature used for a meeting request, as compared to a precursor to an actual IDE.

There is no regulatory obligation whatsoever to submit a pre-IDE. Traditionally, OIVD has welcomed companies to submit pre-IDEs, recognizing that early discussions about the product can benefit both OIVD and the applicant. (Indeed, in some settings, OIVD officials

“strongly encourage” companies to make pre-IDE submissions.) Although pre-IDE meetings do have some significant limitations, they can help applicants avoid costly errors, which can also mean less wasted time for OIVD.

A company should submit a pre-IDE meeting request in writing at least 60 days before the proposed meeting dates. The submission should clearly identify the proposed issues that the company wishes to discuss. These issues need to be carefully and thoughtfully set out. Companies should define the issues precisely and not include too many. These meetings will be relatively brief—usually 60 or 90 minutes—and having too many issues will mean insufficient time to cover each item. Typical topics could include proposed intended use, regulatory pathway (which as described above can hinge on the intended use), clinical study design and proposed analytical validation plans. Of course, the specific topics will be highly dependent on individual circumstances, so contents will vary. Peripheral issues should generally be avoided. OIVD does have a pre-IDE template available.

OIVD will often hold pre-IDE meetings in person. Lately, there has been more of a tendency to hold these meetings by telephone because conference calls place lower demands on OIVD’s resources. While phone calls may work well for a narrow issue, they do not seem as productive for more far-reaching, complex discussions. Sometimes, when the issue is narrow and well-defined, the company itself may prefer to request a telephone conference rather than a meeting. This can have the advantage of getting FDA feedback more rapidly and at less cost.

OIVD cannot provide guidance to these questions unless it has sufficient background information prior to the meeting. A meeting will be of very limited utility unless OIVD has the opportunity to review in advance sufficient background information regarding the proposed application. Conversely, the company should avoid deluging OIVD with too much paper. An overly voluminous pre-IDE can obscure the key issues and also inadvertently raise side issues.

During the meeting, it is important to try to achieve resolution on the issues. Leaving a pre-IDE meeting with a general sense that OIVD is “supportive” is not productive; the goal is to get concrete answers to concrete questions.

This can be easier to say than accomplish. Some issues will not be susceptible to definitive answers at the pre-IDE stage. For example, OIVD may say that the suitability of the *de novo* route cannot be determined until the data have been submitted. Or OIVD may give general comments on a protocol outline, but without concurring in all aspects of the protocol.

Consensus can be elusive. It is important to document the areas of agreement through written minutes provided to OIVD. Typically, OIVD will review and comment upon the draft minutes supplied by the company.

Even concurrence is not necessarily binding. OIVD's statements at pre-IDEs do not have legal force or effect.⁵⁵ Although OIVD does not seem to lightly reverse its concurrence in the plans submitted through the pre-IDE process, concurrence at a meeting does not ensure OIVD will take the same position once the application is submitted. Companies should be alert for signs that a change in policy occurred after the pre-IDE, e.g., the issuance of a relevant draft guidance that may be at odds with the discussion, rather than assuming that the agreement is written in stone.

While positive comments by OIVD cannot always be relied upon, objections are less likely to subside. Put into diagnostic terms, the negative predictive value of a pre-IDE meeting is greater than its positive predictive value. If OIVD is skeptical about some aspect of the study, a company would be ill-advised to brush off those concerns and assume that they will dissipate with time. The concerns may be expressed not just as objections ("we don't agree with your statistical plan"), but also as reservations ("it's not clear that your statistical plan is appropriate" or "why haven't you considered X"). Substantive negative comments and questions must be carefully weighed and addressed.

The pre-IDE process certainly does not guarantee a successful application. There are many potential pitfalls along the way. Even if the study goes according to the plan described to OIVD and the data meet expectations, it is still possible that FDA will not clear or approve the application. Nevertheless, the pre-IDE process is one of the tools available for improving the odds of regulatory success when a company is contemplating a marketing submission for a novel product.

C. Intended Use

As noted above, the concept of "intended use" plays a key role in the regulatory process for IVDs. For example, it can determine whether a product is actively regulated or is essentially unregulated. Some instruments may be sold as general laboratory products, and hence virtually unregulated by FDA.⁵⁶ The same instrument faces active regulation as a device if the manufacturer claims it can be used diagnostically.⁵⁷ Intended use can also determine whether an IVD requires a 510(k) or a PMA.⁵⁸ Even within the 510(k) category, the level of data needed to support the application can vary as a function of the specific intended use.

A recent illustration of how subtle differences in wording can have a major regulatory impact comes from FDA's handling of two different ovarian cancer test applications. In one case, the product was intended for use by physicians who had identified a mass which was going to be surgically removed, and the results of the test would, if positive, suggest that the surgery should be performed by an oncological surgeon. Because the test results could lead to a referral from the generalist who would otherwise do the surgery to a specialist,⁵⁹ the test was perceived as being lower risk and the product was cleared through the *de novo* classification process.⁶⁰ A second ovarian cancer test sought clearance for an intended use in which it could lead oncological surgeons to refer the patient to the general surgeon. This 510(k) was sent by FDA to an advisory panel for review.

The panel members viewed this as a higher risk intended use, because it could result in some patients being referred from the specialist to the generalist.⁶¹ Thus, even though the sponsor submitted data indicating good performance, this product was viewed by OIVD as being relatively high risk. Hence, two ovarian cancer tests intended for similar kinds of adjunctive use in women with known masses who were already going to have surgery were evaluated very differently because one was intended as an aid in referring from the generalist to the specialist, and the other from the specialist to the generalist.

More generally, a test with an intended use claim of “ruling in” a disease will be reviewed differently than “ruling out.” The analyte, test method, disease and patient population may be the same, but the data requirements will still differ—and perhaps even the regulatory pathway—between these similar intended uses. Seemingly minor word choices can have a major impact on multiple aspects of the regulatory process.

Furthermore, the data that are generated in a clinical study must match up with the intended use population. Sometimes, for example, companies will have generated data from a different population than the one covered by the proposed intended use. Studying a group of samples from individuals known to have cancer may not be sufficient to support a screening claim, since the characteristics of individuals with known cancer, e.g., late stage cancer, may be different from the early stage cancers that would be encountered in a general population screening claim. An infectious disease IVD that is studied solely in a high prevalence population may not yield appropriate data for an assay intended to be used to screen a low-risk, general population.

Similarly, the text of the 510(k) or PMA submission should be consistent with the intended use. If the proposed intended use relates to confirming that a patient does not have a disease,

i.e., the assay has a high negative predictive value, then the application should not emphasize the importance of being able to detect the disease.

D. Intended Setting for IVDs

The clinical intended use, e.g., quantifying blood glucose, is a paramount concern during the regulatory review process, but not the only one. IVDs can be intended to be used in different settings and by individuals with different levels of skill. This aspect of intended user can also play a significant role in the regulatory process.

Many IVDs are tests ordered by physicians and are intended for use by laboratories. In that setting, a healthcare professional will integrate the results with other clinical information, and the assay will be performed by trained individuals. Some IVDs, though, are intended for over-the-counter (OTC) use. Examples include glucose, cholesterol and pregnancy tests.

Obtaining 510(k) clearance for OTC use requires careful planning. A company that has 510(k) clearance for a prescription IVD will need to submit a new 510(k) to market the product for OTC use.⁶² The company will need to provide data demonstrating that the IVD is appropriate for use by consumers, without any assistance by a healthcare professional.

One key aspect is whether consumers can operate the product itself. This requires that the product be simple to use. The applicant will also need to show that consumers can interpret the test results without help from anyone else.⁶³

A different setting-related claim is for point-of-care (POC) use. Here, the test is used by individuals in a medical facility outside the laboratory, albeit not by consumers.⁶⁴ Because the users are not limited to trained laboratorians, the applicant will need to establish that the test can be performed by individuals in a nonlaboratory setting. Establishing this level of performance requires clinical studies with actual untrained users.

Obtaining clearance for POC may not be commercially sufficient because POC tests are intended to be used outside laboratories that handle complex tests, such as physician office laboratories (POLs). Under the Clinical Laboratory Improvement Amendments (CLIA), these tests need to have “waived” status to be used in these POLs. Obtaining a CLIA waiver requires a separate application to FDA, submitted after 510(k) clearance is obtained for the IVD, that includes data from studies with the intended group of users of the IVD. Because of differences in legal standards, obtaining “waived” status for the IVD under CLIA can be harder than obtaining POC clearance through the 510(k) process.

VI. Post-approval Issues

A. Marketing

As discussed above, the intended use for an IVD can dictate both the type of premarket application or notification that must be submitted and the amount/type of data that must be developed. Intended use also controls the marketing claims that may be made by an IVD manufacturer for its product. An IVD company must promote its product in a manner consistent with the cleared or approved intended use. Once the clearance or approval is obtained, the essential parameters of the marketing claims are set. They cannot be revised until FDA either clears a new 510(k) or approves a PMA supplement. Given how long this may take, it is critical that sales and marketing personnel provide some input on the proposed intended use, particularly for more novel assays. The failure to integrate commercial and regulatory objectives can result in a clearance or approval that has little commercial appeal.⁶⁵ Conversely, trying to accommodate an overly broad and aggressive intended use because it will have more commercial appeal can result in the failure to obtain any clearance or approval at all.

The difference between intended use and indications for use is not always clear. Sometimes, the two terms are used almost interchangeably. The terms are, in fact, different although they do overlap. Intended use is defined as “the objective intent of the persons legally responsible for the labeling of devices. The intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article.”⁶⁶ In contrast, indications for use delineate the conditions or diseases being tested; prescription or OTC status; the part of the body being tested (e.g., arm or finger); frequency of use; and the patient population.⁶⁷

Another parameter is the type of specimen to be tested. IVDs can be used in a wide variety of biological matrices, such as blood, urine, saliva, hair and fecal matter. There can be even finer subdivisions—blood tests can analyze serum, plasma and/or whole blood. The product application and the label will need to specify which biological materials are intended to be tested.

B. Manufacturing

IVDs are subject to the Quality System Regulation⁶⁸ that applies to other devices. The basic objective is the same: establish requirements that maximize the likelihood an IVD will be manufactured in a manner that results in its performing in a reliable, safe and effective manner.

The QSRs are, on their face, no different for IVDs than for any other type of device. Nothing in the regulation distinguishes IVDs from other devices. Thus, when seeking guidance, IVD

companies can draw upon information applicable to devices generally to better understand interpretations of the QSRs. For insights that may be even more directly pertinent to a particular product, companies should keep abreast of warning letters issued to IVD manufacturers. For example, a warning letter issued in 2009 cited an IVD manufacturer for its alleged failures to follow QSRs, including failure to maintain complete procedures for accepting or rejecting devices, not adequately controlling products that fail to conform to specifications, the absence of “completely defined procedures for implementing corrective and preventive actions,” and not identifying “acceptance criteria for design outputs.”⁶⁹

Most IVDs need to be manufactured in compliance with all the elements of the QSR. There are, however, some low-risk Class I IVDs that are required to meet only two elements of QSRs: recordkeeping and complaints.⁷⁰ IVDs that are subject to this lighter level of regulation include endotoxin assays.

There is a major institutional distinction between enforcement of QSRs for IVDs and for other devices. OIVD has a Division of Patient Safety and Product Quality which is located within OIVD. Both the Director of Patient Safety and Product Quality and the Director of the review divisions report to the Director of OIVD. One of the goals in creating this structure was to have closer integration between the review and enforcement functions. This, in fact, has been the case. IVD companies will often find that both review and compliance officials are concurrently involved in an enforcement matter.

QSR compliance is not required in order to obtain 510(k) clearance. An IVD may be found substantially equivalent even though it is not manufactured in conformance with the QSRs.⁷¹ Of course, the IVD must be manufactured in accordance with QSRs when it is introduced into commerce. An IVD in commercial distribution is adulterated if it does not meet QSRs.⁷²

QSR conformance must be demonstrated in order to obtain PMA approval. This will generally necessitate a pre-approval QSR inspection by FDA. According to FDA’s policy, the inspection should occur within 90 days of filing of the PMA.⁷³ A company whose PMA is otherwise approvable but does not meet QSRs will receive a letter stating that the PMA will be approved once the QSR issues are resolved.

C. Labeling

In general, FDA’s device regulations established very few labeling requirements. IVDs are the one type of product which does have detailed labeling requirements.⁷⁴ For example, IVD labeling must provide information regarding the conditions of storage, instructions for

use, expected values of the test, the details of calibration, known interfering substances and test procedures. These requirements can lead to the generating of a lengthy and complex “Instructions for Use” document that accompanies many IVDs.

During the 510(k) and PMA review processes, OIVD will review proposed product labeling. It is therefore important that the application contain the requisite information. Moreover, the failure of a marketed IVD to comply with the labeling regulations can result in the misbranding of the product.

Endnotes

* Mr. Gibbs has represented some of the companies described in this chapter.

1. See, for example, *eProtein* newsletter (December 2009), sponsored by the National Cancer Institute available at http://proteomics.cancer.gov/objects/pdfs/CPTC_Newsletter_120809-508.pdf. The field described in the newsletter, clinical proteomics, bordered on science fiction only a few years ago.
2. The LEWIN GROUP, INC., THE VALUE OF LABORATORY SCREENING AND DIAGNOSTIC TESTS FOR PREVENTION AND HEALTH CARE IMPROVEMENT 3 (September 2009) available at http://www.labresultsforlife.org/briefing/Lewin_ACLA_Value_of_Lab_Sx_Dx_Report.pdf.
3. One of the open questions is how FDA should regulate diagnostic products generally. See, e.g., Comments and proposal submitted by the Advanced Medical Technology Association to Docket No. FDA-2008-P-0638, Regulation of *In Vitro* Diagnostic Tests (Mar. 27, 2009).
4. Some assays and instruments are exempt from the premarket process altogether, e.g., 21 C.F.R. §§ 864.7040 (adenosine triphosphate release assay) and 868.5580 (oxygen mask). This exemption can be lost, however, under various circumstances, such as a significant change in technology. See *id.* §§ 862.9, 864.9 and 866.9.
5. This does not mean the path for clearance for older tests is always smooth. IVD companies report with increasing frequency that data deemed sufficient just a few years ago is sometimes not adequate now to obtain 510(k) clearance for a new version of the IVD.
6. IVDs encompass both assays and the instruments that run the assays. For simplicity, this chapter will focus on assays. The basic regulatory requirements and procedures also apply to instruments, although there are certainly some unique issues, e.g., the need to have at least one assay cleared for use on the instrument.

7. FY 2005 OIVD Annual Report – Part 3 – Key Performance Indices *available at* <http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm126877.htm>. This is the most recent year with publicly available clearance and approval data.
8. 21 U.S.C. § 360c(i)(1)(A)(ii).
9. *Id.* § 360c(i)(1)(A) (emphasis added).
10. OIVD does not review all IVDs. Certain IVDs, such as assays used in blood-banking, are regulated by the Center for Biologics Evaluation and Research (CBER). The legal requirements that apply to CBER review of IVDs are the same legal requirements that govern IVDs regulated by OIVD. The manner in which those legal requirements are applied, though, does differ.
11. *See discussion infra* regarding pre-IDE meetings.
12. Instruments that are sold as RUO products cannot support a 510(k) clearance for an assay designed to work on that instrument. Although some 510(k)s have been cleared that referenced RUO instruments, OIVD has indicated that it does not believe this to be lawful.
13. Devices are placed into Class I (low risk), Class II (moderate) and Class III (high). In general, Class III devices need to obtain PMA approval.
14. Press Release, Food and Drug Administration, Institute of Medicine to Study Premarket Clearance Process for Medical Devices (Sept. 23, 2009).
15. FDA, *CDRH To Abandon Bad Precedents On Path To Predictable 510(k)s*, THE GRAY SHEET (Dec. 21, 2009).
16. 21 U.S.C. § 360c(i).
17. *E.g., Draft Guidance for Industry and FDA Staff, Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Human Papillomaviruses* (Sept. 9, 2009) *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm181511.pdf>.
18. Perhaps not surprisingly, ascertaining what is “truth” can be complex. This has led to standards being described in evocative if not scientific terms: “gold,” “tarnished gold,” “silver,” etc.
19. The technical definitions of terms such as “sensitivity” and “specificity,” as well as the details of the kind of data needed to support these various claims, are outside the scope of this article. For more information, *see Guidance for Industry and FDA Staff, Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests* (Mar. 13, 2007) *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071287.pdf>.

20. *Id.*
21. Applicants may choose instead to state that they will make a copy of the 510(k)—sans confidential information—available to requestors. 21 C.F.R. § 807.93. This option is rarely used.
22. *See, e.g.,* FDA Decision Summary available at http://www.accessdata.fda.gov/cdrh_docs/reviews/K092283.pdf.
23. A new, intriguing resource is a “Mock 510(k)” prepared by the National Cancer Institute for a made-up IVD. This publicly available document contains a fictitious but comprehensive 510(k). A companion document provides OIVD’s response, which yields some useful insights. *See* Fred E. Regnier, Purdue Univ., “SDIA 510(k) Filing—A ‘Mock 510(k)’ for a [sic] ‘An Immunological Array Platform for Simultaneous Assay of Multiple Glycoprotein Isoforms’” (undated). *See also*, F. Regnier et al., *Protein-Based Multiplex Assays: Mock Presubmissions to the U.S. Food and Drug Administration*, 56 CLIN. CHEM. 165-71 (2010).
24. 21 C.F.R. § 20.40.
25. A copy of the guidance document may be found on FDA’s website at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094533.htm>.
26. *Guidance for Industry and FDA Staff, Recommendations for Anti-Nuclear Antibody (ANA) Test System Premarket (510(k)) Submissions* (Jan. 22, 2009) available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092750.pdf>.
27. *510(k) Submissions for Coagulation Instruments—Guidance for Industry and FDA Staff* (June 19, 2003) available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070940.pdf>.
28. 21 C.F.R. § 10.115(d).
29. *See, e.g.,* *Draft Guidance for Industry and FDA Staff, Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses* (Feb.15, 2008) available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071458.pdf>.
30. A company might, for example, submit a 510(k) for the same type of assay, because it wants to make changes that would significantly affect safety or effectiveness. *See* 21 C.F.R. § 807.81(a)(3)(ii).
31. FDA, *FDA Diagnostics Office to Tighten Its Control, New Chief Says at AACC, THE GRAY SHEET* (July 23, 2009).

32. OIVD reviewers will sometimes say that the review memoranda on FDA's website provide notice to companies of FDA requirements. Whether this is a lawful—or even reasonable—means of communicating data requirements is debatable.
33. When OIVD believes that the 510(k) should be cleared but there is a) a substantial risk of off-label use and b) that off-label use may present clinical risks, the 510(k) can be cleared with “limitations.” 21 U.S.C. § 360c(i)(1)(E).
34. 21 C.F.R. § 10.75.
35. 21 U.S.C. § 360c(f)(2). Automatic reclassification is distinguished from the process for reclassifying a device that has already been classified, a long and cumbersome process.
36. FDA, *New Section 513(f)(2)—Evaluation of Automatic Class III Designation, Guidance for Industry and CDRH Staff* at 1 (Feb. 19, 1998) available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf>.
37. *Id.* at 1-2.
38. *De novo* status can be meaningfully evaluated only within the context of a specific intended use. Thus, this discussion can be productive only if the intended use is final, or close to final.
39. *See, e.g.*, Guidance Document for the Submission of Tumor Associated Antigen Premarket Notifications, [510(k)], to FDA (September 19, 1996) available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094111.htm>.
40. FDA, Search for Releasable 510(k) Database available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm>.
41. Companion diagnostics are discussed at length in Chapter 8.
42. DakoCytomation Her2 FISH pharmDx™ Kit Labeling (P040005) available at http://www.accessdata.fda.gov/cdrh_docs/pdf4/P040005c.pdf.
43. This does not mean all IVDs intended to help guide drug choices will go through the PMA process. *See, e.g.*, Verigene® Warfarin Metabolism Nucleic Acid Test (K070804); Press Release, Food and Drug Administration, FDA Clears Genetic Lab Test for Warfarin Sensitivity (Sept. 17, 2007). The precise intended use plays a pivotal role in whether the companion diagnostic is reviewed as a 510(k) or PMA.
44. 21 U.S.C. § 360e(d)(1)(A).
45. *See* Guidance for Sponsors, Institutional Review Boards, Clinical Investigators and FDA Staff, Guidance on Informed Consent for In Vitro Diagnostic Studies Using Leftover Human Specimens that are Not Individually Identifiable (Apr. 25, 2006) available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071265.pdf>.

46. Several advisory panels may review IVDs, including the Hematology and Pathology Devices Panel, Immunology Devices Panel, Microbiology Devices Panel, or the Molecular and Clinical Genetics Panel.
47. OIVD also periodically convenes panel meetings outside of PMA reviews to discuss scientific issues. These transcripts can also be an important source of information. *See, e.g.,* Hematology and Pathology Devices Panel Meeting (July 18, 2008) (discussing waiver issues for point of care tests). There are even occasional panel meetings to review 510(k)s.
48. *See discussion, infra.* One topic that the applicant should consider including on the agenda is the statistical analysis plan.
49. Barry Meier, *F.D.A. to Seek New Standards on Human Test Data*, N.Y. TIMES, December 30, 2009, at B1. *See* S. Dhruva, et al., *Strength of Study Evidence Examined by the FDA in Premarket Approval of Cardiovascular Devices*, JAMA 2009; 302(24): 2679-85 (criticizing the PMA review process).
50. *See* 21 C.F.R. § 814.39.
51. Modifications to Devices Subject to Premarket Approval (PMA)—The PMA Supplement Decision-Making Process (Dec. 11, 2008) *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089360.pdf>.
52. Letter from Bradley Thompson to FDA regarding “Guidance Document Submission,” FDA Docket No. 03D-0334 (June 17, 2003) *available at* <http://www.fda.gov/ohrms/dockets/dailys/03/jul03/072403/03d-0334-gdl0001-vol1.pdf>.
53. *See also*, HiFi DNA Tech LLC v. Dep’t Health & Human Services, No. 09-1832-cv, Summary Order (2nd Cir. December 17, 2009).
HiFi alleged that FDA acted arbitrarily and capricious when it reviewed its product as a cancer-detection device instead of a virus-detection device. The court found, however, that based on the intended use for the device as defined by HiFi in its FDA application, the agency reasonably determined that the device’s intended use was to assess a woman’s risk of developing cancer.
Posting of Carmelina G. Allis, Court of Appeals Upholds Lower Court’s Ruling in HiFi’s reclassification Petition Denial Case, *FDA Law Blog*, http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2009/12/update-court-of-appeals-upholds-lower-courts-ruling-in-hifis-reclassification-petition-denial-case.html (December 22, 2009, 13:24 EST).
54. Guidance documents are not legally binding, and, as a matter of law, an applicant can try to use other means to satisfy the 510(k) requirements. 21 C.F.R. § 10.115(d). This legal right notwithstanding, an applicant whose approach diverges materially from the approach described in the guidance document may be well-advised to discuss that approach with OIVD in advance.

55. 21 C.F.R. § 10.85(k).
56. 21 C.F.R. § 862.2050. General laboratory equipment is exempt from the need for a 510(k) and from virtually all QSR requirements.
57. Another scenario is that an instrument will be unregulated if intended for forensic testing for the detection of drugs of abuse, but will require a 510(k) if intended to detect drugs of abuse in the workplace or home. *See, e.g.*, 63 Fed. Reg. 10,792, 10,793-94 (Mar. 5, 1998); 68 Fed. Reg. 18,230 (Apr. 7, 2000).
58. *See* “Biomarkers and FDA Regulation of In Vitro Diagnostic Devices” (May 20, 2009) (presentation by Robert L. Becker Jr., M.D., Ph.D., Office of In Vitro Diagnostic Device Evaluation and Safety, FDA, at the Am. Ass’n. of Clinical Chemistry Audio Conference – Personalized Medicine and the Clinical Laboratory – What the Future Holds).
59. Studies have shown that women with ovarian cancer have better outcomes when the surgery is performed by an oncological surgeon than a general surgeon.
60. *See* Vermillion, Inc’s OVA1™ Test (K081754). The full actual intended use statement is quite complex.
61. For example, one panel member stated,

My concern is with the false negatives. And I know how devastating this disease is. I know it firsthand, and I know how poor my prognosis is. If I were told that there was, say, a 10 percent chance that I could have this terrible disease and, you know, I was given the option of you can either stay here and be comfy in your own community and have just a GYN or a general surgeon do this or you can go to, you know, a more major center and have a specialist do it, I would certainly choose the specialist, even if my risk was low. It’s that choice that I’m worried about.

FDA Immunology Devices Panel Meeting Transcript at 108-9 (Dec. 3, 2008).
62. While perhaps theoretically possible, few, if any, Class III IVDs would be suitable for OTC status due to the riskiness of the product that presumably caused it to be placed into Class III in the first place.
63. Assessing the Safety and Effectiveness of Home-Use In Vitro Diagnostic Devices (IVDs): Draft Points to Consider Regarding Labeling and Premarket Submissions (October 1988) *available at* <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094277.htm>.
64. POC tests can offer significant health benefits by providing much more rapid information to the clinicians. At the same time, POC tests may not perform quite as accurately as IVDs run in a laboratory. In evaluating this trade-off, it is important to assess the clinical value of faster, albeit perhaps somewhat less accurate, information. *See* STEVEN D. LEVITT & STEPHEN J. DUBNER, SUPERFREAKONOMICS 69-74 (2009) (discussing the critical need for timely information in emergency medicine).

65. Integrating the intended use with reimbursement coverage can also be an important objective, but one that is outside the scope of this chapter.
66. 21 C.F.R. § 801.4.
67. *Id.* § 814.20(b)(3)(i). *See also*, FDA Guidance Document, Deciding When to Submit a 510(k) for a Change to an Existing Device at 24 (Jan. 10, 1997) (defining “intended use” and “indications for use”) *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080243.pdf>.
68. 21 C.F.R. Part 820.
69. Warning Letter to Abbott Laboratories (Aug. 12, 2009).
70. *Id.* §§ 820.180 and 820.198. In addition, most Class I devices are exempt from the design control requirement.
71. 21 U.S.C. § 360c(i)(1)(D) (FDA “shall only request information that is necessary to making substantial equivalence determinations”).
72. *Id.* § 351(h).
73. The Review and Inspection of Premarket Approval Applications Under the Bioresearch Monitoring Program at 8 (Jan. 8, 2008) *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071567.pdf>.
74. 21 C.F.R. § 809.10.