

Originally Published [IVD Technology](#) May 2005**Commentary****Exploring other options****Part 1: The trend toward alternative market pathways****Jeffrey N. Gibbs**

IVD companies enjoy a wealth of different alternatives for commercializing new technologies. Most other medical device companies do not have any equivalent options since only one pathway is available for them to enter the market. Without FDA approval or clearance, most new medical products cannot be commercialized.

Meanwhile, an IVD company could achieve early market penetration and adoption of its technology through various means that entail no FDA action. For example, a company may sell one or more components as analyte specific reagents (ASRs). The IVD manufacturer may partner with a reference laboratory that uses its technology or components to develop a home-brew assay. Alternatively, the manufacturer could establish its own CLIA-certified lab to commercialize its products as in-house assays.

Under FDA regulations, some early-stage IVD products that do not have a known intended use and an established clinical utility can be distributed for research use only (RUO). Other RUO products are sold to pharmaceutical companies for use in clinical studies. Yet other test kits may be sold to various facilities as investigational use only (IUO) products.

In some cases, IVDs may enter the market or be cleared with a limited clinical indication for use. Such IVDs may be utilized later for more clinically important purposes after additional relevant clinical data are generated. Many immunohistochemistry (IHC) staining techniques apply this pattern of initially entering the market with a narrow use and therefore an exemption from FDA clearance as a Class I device, followed by broader adoption for more-expansive uses, either off label or with FDA approval clearance.

These regulatory options are not mutually exclusive. An IVD company can sell ASRs to CLIA high-complexity laboratories, use the same components in its own lab to make a home-brew test, and sell a kit containing the components as part of a clinical study.

The availability of different regulatory options does not mean they are of practical importance. Differences exist between a regulatory pathway appearing in a statute and that pathway being viable.

For example, product development protocols (PDP) have been included in the statute since 1976. Despite a reengineering effort by FDA's Center for Devices and Radiological Health (CDRH) in the late 1990s to stimulate its use, the PDP process has proven to be so cumbersome that it has rarely been used and is now relegated to a historical footnote. Even though Congress spent hundreds of words describing PDPs, the process has become irrelevant.

However, the multitude of regulatory pathways for IVDs is of great significance. While not valuable to every manufacturer or applicable to all products, they provide not only the means by which many new diagnostics enter the marketplace but also the route by which many clinically important tests initially become available. For many IVD companies, particularly firms with new and innovative technologies, using alternative pathways is becoming more common.

While the use of alternative regulatory methods seems to be accelerating, this trend raises some profound questions. For example, why do certain IVD companies delay or bypass altogether obtaining FDA premarket authorization? Should changes be made to the regulatory structure? What are the long-term implications for FDA and the IVD industry of the more widespread adoption of alternative routes to market? This article will discuss this growing tendency to explore and use such routes rather than obtaining FDA marketing clearance.

**RUO, IUO, and Off-Label Use**

Jeffrey N. Gibbs, JD, is a director at Hyman, Phelps & McNamara, a Washington, DC-based law firm, and is a member of IVD Technology's editorial advisory board. He can be reached at [jng@hpm.com](mailto:jng@hpm.com).

The introduction to the market of IVD tests that have not undergone FDA review is nothing new. For example, the creation of new tests by laboratories for their own in-house use is a well-entrenched practice, significantly predating the Medical Device Amendments of 1976. For decades, IVD companies have been selling components to labs for use in developing home-brew tests. The final IHC regulation also ensured that most antibodies used in IHC staining would be Class I exempt.<sup>1</sup>

In the late 1980s and early 1990s, the use of RUO and IUO kits proliferated, and these types of labels are still routinely used. While FDA regulations permit RUO and IUO products to be distributed only under strict conditions, those regulations are not always followed. A review of Web sites shows a number of IVD companies distributing RUO and IUO products that do not appear to meet the regulations.

It is unclear what enforcement actions FDA has taken against such companies since the agency does not publicly disclose all enforcement decisions. It is also unclear what actions FDA may take in the future concerning this long-standing issue. IVD companies that improperly distribute RUO and IUO materials do face the possibility of enforcement actions as well as civil liabilities in the event of patient injuries. Nevertheless, companies are still distributing RUO and IUO products outside the terms of FDA regulations.

Off-label usage presents a variation on this theme. Once an IVD product has been cleared or approved for one use, it can then be used for other applications. Sometimes, such unlabeled applications eclipse the labeled uses in volume and clinical significance. There is nothing improper under the Federal Food, Drug, and Cosmetic Act about clinicians or laboratories using IVDs for off-label indications. Congress expressly endorsed off-label use of medical devices in passing the FDA Modernization Act of 1997.<sup>2</sup>

However, even though off-label use of an IVD is legal, a lab or clinician can face civil liabilities if that use results in patient injuries. In addition, while off-label use is appropriate in the practice of medicine, IVD manufacturers may not advertise their products for use in this manner. Improper promotion of an IVD for off-label use can render the device adulterated and misbranded, leaving a manufacturer subject to enforcement actions. Regardless, IVD manufacturers can and do take into account possible off-label applications for their products when developing products, performing market assessments, and developing regulatory strategies.

An example of an IVD test that is widely used off label is the triple-marker test for prenatal screening of Down's syndrome. Consisting of an evaluation of the relative values of alfa-fetal protein, estriol, and human chorionic gonadotropin (hCG), the combined use of these markers for screening is not FDA approved, even though each of the individual tests is either cleared or approved for other purposes. An IVD company that wanted to sell the three tests together with a screening claim would need to obtain approval. So far, no company has done so.

Nevertheless, the triple-marker screening test is the widely adopted standard of care. Reference and state laboratories run this test, and it is a routine practice for many obstetricians to order this test. Since it has become common to order this unapproved test for certain pregnancies, physicians who fail to prescribe it might face malpractice litigation if a baby is born with Down's syndrome. Consequently, an IVD test has become ubiquitous in its use despite the lack of FDA authorization. Given the anticipated difficulties of obtaining a premarket approval (PMA) for a triple-marker screening kit and the lack of commercial advantages in spending the money to get approval, it seems unlikely that FDA approval clearance will be forthcoming.

### **A Shift in the Regulatory Approach**

The existence of nonapproved IVD tests entering routine clinical practice is not new or newsworthy. What is striking is how prominent and prevalent some of the tests have become. For example, laboratories offer a widely publicized and prescribed screening test for genetic mutations associated with breast and ovarian cancer, which has not undergone FDA review. A newer home-brew test is used to help physicians decide whether to initiate chemotherapy for patients who develop breast cancer.<sup>3</sup> State legislatures are mandating the testing of newborns for genetic disorders, even though some of the tests have not received FDA approval.<sup>4</sup> Labs offer batteries of tests for genetic mutations that may cause neurological disorders, again without FDA review or approval. Laboratories have commercialized several different Alzheimer's tests as home-brew tests. A widely publicized test has recently become available for use in predicting chemotherapy responses in women with breast cancer.<sup>5</sup>

With the advent of genomics technology, nanotechnology, proteomics, and other technological advances, the number, variety, and potential clinical importance of nonreviewed assays is growing. The number of home-brew genetic tests dwarfs the number approved by FDA. While some of the tests are pure home brews, many incorporate materials produced by IVD manufacturers. FDA has indicated an interest in clarifying its regulatory approach toward such unapproved tests and ASRs, but the outcome and timing of the agency's review are uncertain.

Even though potential regulatory changes may add uncertainty to using alternative methods for commercialization, an increasing number of manufacturers are adopting such methods. These developments represent an important shift in the regulatory approach taken by IVD companies. When developing new product commercialization strategies, IVD companies no longer consider obtaining FDA clearance as the only route for their tests.<sup>6</sup> Many companies now assess not only FDA authorization but also other options that may enable a more-rapid market diffusion of their new tests. For new technologies or analytes, IVD companies will look at whether to commercialize the product in whole (RUO, IUO, home brew) or in part (such as an ASR) without first obtaining FDA marketing authorization. In business strategy and product development meetings, IVD

companies will sometimes discuss not only the requirements for getting FDA approval but also the alternative routes to commercialization (e.g., partnering with laboratories). Indeed, the discussions may focus as much upon alternative strategies as FDA regulatory pathways.

Even though IVD companies review alternatives to FDA authorization for market entry, they often do not appear to consider such authorization as being either optional or unimportant. On the contrary, many well-recognized benefits are obtained from FDA marketing clearance. For example, advertising and promoting a 510(k)-cleared or approved test kit are easier than selling an ASR, RUO, or IUO kit (e.g., performance claims can be made). While Class I, 510(k)-exempt IHCs can only make adjunctive claims, FDA clearance can enable more-powerful marketing claims. Home-brew assays offered by a company's laboratory have less market access and penetration than a kit that can be sold to any laboratory.

In addition, FDA approval offers credibility to the financial and investment communities that the other regulatory options cannot match. FDA clearance helps in gaining access to overseas markets, particularly to non-tier I countries with limited government oversight of IVDs and where FDA approval is often viewed as the gold standard. Obtaining reimbursement coverage for premarket-approved IVDs can be easier, and they are less likely to give rise to successful product liability suits.<sup>7</sup> And at least for PMA devices, companies can tout their products as being FDA approved. For some new products, IVD manufacturers will conclude that FDA marketing authorization is the most attractive way to enter the market.

Moreover, alternative regulatory pathways are not always available for every new diagnostic assay. For example, not all diagnostic kits can be separated into constituent components that qualify as ASRs. In addition, ASRs are subject to many restrictions on marketing and packaging, which do not apply to test kits. Similarly, RUO and IUO products are not equivalent to kits that receive FDA marketing authorization and are subject to significant regulatory restrictions. For example, while IUO products are permitted at least limited commercialization, the results generated are meant for studying intended uses, and should be reported to patients only in the context of actual clinical studies and with institutional review board oversight and informed consent.

All alternative routes carry some significant regulatory restrictions and commercial limits compared with 510(k) clearance or a PMA. They are also subject to possible FDA sanctions if the agency concludes that the IVD products are being improperly commercialized. The likelihood of FDA action increases if such products are believed to present higher potential clinical risks.

### Considering Parallel Paths

Despite the very real advantages of FDA authorization as noted above, many new IVD tests now first reach the U.S. market through alternative regulatory means. This phenomenon is not limited to small companies that have few resources. Large IVD manufacturers also utilize alternative methods. Both large and small IVD companies that have developed new technologies or entirely new diagnostic tests regularly wish to discuss what options exist for expediting access to the marketplace. Although the cost of traversing the FDA process also plays a role, particularly for novel products, the primary motivations appear to be speed and predictability.

The exploration of other regulatory routes does not stem from a desire to circumvent FDA or a fear of dealing with the agency. In fact, many IVD companies that are using or evaluating other options have successfully navigated through the FDA process in the past. In addition, they are either concurrently seeking approval or clearance for other assays, or planning to obtain FDA authorization for one or more products in the future. Nonetheless, companies are also exploring other routes because they believe that the process to generate data for their new analytes or new technologies will take years to complete, and there is no assurance that the FDA review process will ultimately be successful.

An example of the trend to consider parallel paths to market is the OvaCheck by **Correlogic Systems Inc.** (Bethesda, MD), an ovarian cancer test that assesses protein patterns. According to an article published in the New York Times, the company wished to pursue parallel approaches. "OvaCheck's developers plan to conduct a clinical trial to win FDA approval for diagnosing recurrences of ovarian cancer but wish to market now because a trial for an approval as an early-stage diagnostic would take too long."<sup>8</sup> Soon thereafter, FDA objected to the sale of the test to laboratories and posted a letter on the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) Web site indicating the agency's view that this product requires premarket review.

Another example of concurrent paths to market is **Nymox Pharmaceutical Corp.** (Maywood, NJ), whose PMA for its AlzheimerAlert, an Alzheimer's disease diagnostic test, was not accepted by FDA. However, this setback did not render the test unavailable. According to a company press release, Nymox was already using the assay to perform tests through its own laboratory, and it continued to offer the AlzheimerAlert through its own reference laboratory after being rejected by FDA. The company also has not abandoned seeking FDA approval, having recently filed an amendment to its PMA.<sup>9</sup>

### Conclusion

The availability of alternative regulatory pathways notwithstanding, OIVD still receives plenty of new IVD product applications to review. In fiscal year 2004, OIVD cleared 472 510(k)s, and approved 9 original PMAs; in fiscal year 2003, the numbers were 520 and 4, respectively. These numbers understate the total number of new products submitted for review, since they exclude applications that were not cleared or approved, supplements, and amendments. Either way, OIVD reviews and approves an enormous number of new products, including IVDs that embody innovative technologies and medically important new indications.

At the same time, a large number of new assays are being introduced without undergoing FDA review. Moreover, this trend is increasing. Given the importance of the FDA review process, this trend should not be ignored. The second installment of this article will discuss some possible approaches that may lead to more new diagnostic tests being submitted to FDA for review, or being submitted sooner.

## References

1. Code of Federal Regulations, 21 CFR 864.1860(b)(1).
2. Buckman Co. v. Plaintiffs' Legal Comm., 531 S. Ct. 341 (2001).
3. K Garber, "Gene Expression Test Foretells Breast Cancer's Future," *Science* 303, no. 5665 (2004): 1754–1755.
4. Michael Waldholz, "Parents Prod States to Boost Newborn Testing," *Wall Street Journal* (July 30, 2004): B1.
5. G Dutton, "Pharmacogenomic Tests for Breast Cancer," *Genetic Engineering News* 25, no. 2 (2005): 1.
6. W Diller, "In Diagnostics, Is FDA Approval Superfluous," *In Vivo: The Business Medicine Report* 21, no. 4 (April 1, 2003): 2.
7. *Horn v. Thoratec Corp.*, 376 F.3d 163 (3rd Cir. 2004).
8. A Pollack, "New Cancer Test Stirs Hope and Concern," *New York Times* (February 3, 2004): F1.
9. "Nymox Re-files Urine Test Kit for Alzheimer's with FDA," *Clinica* 1136 (December 10, 2004): 18.

Copyright ©2005 **IVD Technology**

Copyright © 2005 Canon Communications, LLC [About Us](#) | [Customer Care](#) | [Advertising Information](#) | [FAQ](#) | [Site Guide](#)