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Commentary

Exploring other options

Part 2: Facilitating the FDA review process

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The first installment of this article (*IVD Technology*, May 2005) explained how IVDs that have not undergone FDA review are proliferating. Even though such tests have not obtained FDA authorization or been cleared for the indications for which they are being used, laboratorians and clinicians need to be able to conduct and order them. Restricting labs to only FDA-cleared IVDs would have adverse medical consequences, particularly since home-brew tests are well entrenched in the clinical decision making process. Nevertheless, the healthcare system's reliance on tests that have not been reviewed by the agency raises some pressing questions.

For example, would the systemic bypassing of FDA have a net positive or negative effect? If many new, sophisticated IVDs enter the marketplace via home-brews or other means and then never undergo FDA review, is that a cause for concern, and does anything need to be done? In other words, if the trend toward adopting non-FDA-approved tests accelerated, would that be a bad thing?

Moreover, what will the ultimate impact be for the IVD industry and innovation if this trend persists? **AdvaMed** (Washington, DC) has weighed in on this issue by arguing that IVD manufacturers are put at a significant competitive disadvantage because of the lower regulatory hurdles for home-brews, and that "the risks posed by lab-made tests that lack FDA oversight cannot be overestimated."[1]

On balance, the FDA review process, which includes careful examination of packaging inserts and product performance, probably does result in better clinical management. Congress certainly made that policy judgment by including IVDs within FDA's jurisdiction.[2] Given that submitting product applications to the agency is in the public's interest, a key question, then, is what regulatory measures can be implemented to induce IVD manufacturers to seek FDA marketing authorization, rather than follow one of the alternative commercialization routes. The agency could take a number of concrete steps that would encourage more manufacturers to seek market access through the FDA review process.

Product Review Processes

For example, FDA could make the review process more predictable. IVD manufacturers would benefit by knowing early in the process whether their new products will be subject to review through the 510(k), premarket approval (PMA), or de novo process. Since predictability matters a great deal to manufacturers, uncertainty may deter those companies that cannot get a clear indication at an early stage of what the agency plans to do.

FDA generally appears to underestimate the costs and side effects of uncertainty in the review process. If IVD manufacturers find out their products are being reviewed differently than had been expected, they are more likely to pursue a non-FDA alternative the next time. Moreover, unexpected late changes in a new IVD's regulatory status can have a ripple effect. IVD manufacturers share their regulatory concerns with other companies, which may then consider other market pathways for their products.

FDA also needs to recognize that PMAs are far more burdensome than 510(k)s for IVD manufacturers. Some agency officials appear to believe that as long as a manufacturer is conducting a PMA-caliber clinical study, the incremental requirements of the PMA process are negligible. However, PMAs are significantly longer, preapproval inspections are taxing and add uncertainty, user fees are much higher, and advisory panels, when necessary, not only cost time and money but also add unpredictability. Moreover, PMAs are even more burdensome once approval is secured (e.g., filing annual reports) and offer less flexibility in making labeling, product, and manufacturing changes.[3] PMAs are much more costly and difficult than 510(k)

s, even when the clinical requirements are no greater.

A relatively new regulatory option is de novo review. This process allows FDA to clear new IVDs via a 510(k) even without a predicate device.[4] De novo review can significantly facilitate market entry and reduce the post-approval workload that the PMA process engenders.

The Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) has been receptive to de novo review by clearing more de novo applications than the rest of the Center for Devices and Radiological Health (CDRH) combined. Given the benefits of de novo review and the suitability of many new analytes to this process, OIVD should further expand its use. Moreover, OIVD should commit to the de novo process at early-stage meetings with IVD manufacturers. Earlier knowledge that this route is available can encourage manufacturers to pursue FDA marketing authorization. Conversely, uncertainty from the agency about the availability of de novo (or 510(k) instead of PMA) can deter IVD manufacturers from going down the FDA approval pathway.

In fact, OIVD is willing to discuss regulatory pathways at early-stage meetings. The information that OIVD provides at this stage is valuable and helps IVD manufacturers formulate their plans for the review process. However, such early discussions do not guarantee predictability. Sometimes, a manufacturer is advised that a pathway is contingent upon the data, which offers little certainty. Occasionally, the pathway may get altered during the review process. While such situations are rare, they can add regulatory complexity and delay for the affected company.

Clinical Studies

The need for certainty also extends to the design of clinical studies to support a premarket submission. The FDA Modernization Act (FDAMA) gives manufacturers the right to ask the agency to agree formally to a protocol which will result in approval if followed.[5] However, this congressionally bestowed provision has been used sparingly. FDA prefers informal understandings.

Although such understandings are often honored, that is not always the case. Knowing that FDA is likely to follow an informal agreement on the parameters of a clinical study (e.g., the number of subjects, endpoints, and data to be collected) may not provide an IVD manufacturer with a high enough level of confidence to justify a large investment in a study, particularly if other, more certain, commercialization options exist. In fact, manufacturers should be aware that an FDA regulation permits the agency to disown virtually any statement made by any of its employees.[6]

While informal agreements are helpful, they do not provide assurances. This point was driven home at a non-IVD advisory panel in 2003. During the panel meeting, a company noted it had used a protocol that FDA had accepted. A division director repudiated those agreements, saying the sponsor should not have relied on the protocol:

Yes, I just want to comment, maybe just because I am from FDA, that it bothers me, the use of the terms “required” and “agreement,” since neither of them are really the case. We have guidances, and that means we provide our recommendations to sponsors, and we have discussions with them about what our best recommendations are about testing to address the issues in that application. But it is not requirements, and “agreement” has a specific meaning to us, where we have an agreement that if they do this, that will get them their approval.[7]

Even though an OIVD official did not make this statement, it does reflect FDA’s strict legal interpretation that a nonstatutory agreement is not binding.

To its credit, OIVD has been receptive to pre–investigational device exemption (IDE) meetings to discuss proposed clinical studies. OIVD has encouraged IVD manufacturers to meet and discuss regulatory pathways and data requirements. (OIVD is now conducting its own evaluation of the value of pre-IDE meetings.[8]) However, CDRH has been reluctant to enter into binding agreements, even though that procedure is specified in FDAMA. For companies and investors looking for a high degree of certainty, there can be a difference between a good-faith commitment and a statutorily defined agreement. While IVD manufacturers can and do rely on commitments given by OIVD during pre-IDE meetings, they are not legally binding. Manufacturers need to know that their data will lead to approval or clearance if the studies meet agreed-upon criteria.

IVD manufacturers that have encountered evolving requirements during a product review may look for alternatives that do not involve FDA when developing their next product. Similarly, altering the data requirements because of changed agency personnel can create difficulties for IVD product sponsors. A manufacturer that was advised that collecting data set X would be acceptable should be able to rely on that statement, even if a new reviewer or statistician joins the review team.

Conversely, real-time reviews can expedite approvals and clearances. Raising and resolving issues with an IVD manufacturer about its clinical study as they are identified can accelerate the review process and improve stakeholder satisfaction.

Having FDA ask questions that it should have asked earlier in the review process is another issue. It is frustrating for an IVD manufacturer to have its 510(k) undergo an extra review cycle because an FDA reviewer did not ask questions the first time. (Such inquiries are distinguished from raising questions about new information provided in the initial reply.) The loss of 90 days or more can be a heavy blow to a manufacturer, and receiving an avoidable not-substantially-equivalent letter because of an extra review cycle is costly.[9] Given how rapidly technology changes, new IVDs can have a comparatively short commercial shelf life.

Data Requirements

FDA's data requirements need to be reassessed, particularly with respect to clinical utility. Obtaining clinical data is one of the biggest stumbling blocks to gaining FDA authorization for new IVDs. Data requirements should be limited to supporting the claims in the packaging inserts as written by the IVD manufacturers. Information regarding potential uses, as opposed to claimed uses, should not be required.[10]

FDAMA directed the agency to apply the least burdensome data requirements for medical devices.[11] CDRH has also issued an implementing guidance.[12] OIVD personnel have quoted this provision in discussions with the IVD industry. Nevertheless, the clinical data requirements that are actually imposed are not always consonant with the least burdensome directive.

One IVD industry proposal that would result in FDA oversight of an IVD's analytical performance but would not require clinical data in order to obtain marketing authorization has encountered a frosty reception. CDRH has been reluctant to accept the request to establish a new regulatory category called in vitro analytical tests (IVAT). Although last year David Feigal, MD, and Steve Gutman, MD, stated that FDA would "continue to consider the IVAT proposal," the agency so far has not been receptive. At the same time, Feigal and Gutman acknowledged the need to consider "new ways of reviewing IVDs based on a total product life cycle approach."[13]

In response to comments on the IVAT proposal, FDA has stated that analytical performance as a basis for premarket clearance is common in cases in which the link between analytical and clinical results is well established. Analytical performance as a basis for clearance is already feasible under current FDA regulations and is being used. The recently cleared cystic fibrosis test apparently relied upon this type of data. However, when clinical use of a new IVD is not well linked to analytical performance, FDA's view is that current requirements would call for a clinical study. While FDA has noted its interest in novel review techniques as they might apply to both its least burdensome and critical path initiatives, the agency's view has been and remains that the safety and effectiveness of IVD devices relate to both analytical and clinical performance.

Greater reliance by FDA on design controls, manufacturing controls, and postmarket controls should enable the review of many applications with less up-front data. The agency can also use its flexible ability to impose special controls on Class II devices for accelerating the review and market introduction of new IVDs.[14]

CDRH's recognition of the need to find new ways of conducting reviews is potentially promising. However, more-concrete actions are required. For IVD manufacturers that have developed novel products, imposing unnecessary clinical data requirements is a major deterrent to pursuing the FDA approval pathway. FDA should accompany its requests for more data with a reasoned explanation for why the data are needed, and should give the manufacturer a prompt, fair opportunity to respond. The agency should utilize alternative approaches, such as narrower labeling and the use of special controls for Class II devices, in lieu of more-elaborate clinical studies. The data requirements should be based on the intended use in the labeling, and not potential clinical applications outside the labeling. Risk-based approaches should be considered. As AdvaMed proposes in its comments on the critical path initiative, unnecessary barriers to obtaining clinical data (e.g., informed-consent requirements for anonymous banked specimens) should also be scrapped.

Other Regulatory Changes

A relatively minor change in policy may also make 510(k)s more attractive. IVD manufacturers can now promote that they have obtained premarket approval.[15] Still, the ability to publicize 510(k) clearance is circumscribed. FDA regulations prohibit manufacturers from creating "an impression of official approval of a device" because a 510(k) was obtained.[16] Allowing IVD manufacturers to advertise that they have received FDA clearance could be an incentive by providing a marketing edge over products that cannot make that claim.

While the focus should be on carrots, the sticks cannot be ignored. For example, while research use only (RUO) products should not be promoted for diagnostic use, a number of IVD manufacturers still engage in that practice. The existence of RUO products directly competing with FDA-cleared devices can serve as a disincentive for going through FDA. If another manufacturer is able to sell unimpeded an unapproved RUO product for the same claims, 510(k) and PMA holders are apt to question the value of their own 510(k)s and PMAs. This is more likely to be the case when a competitive RUO product remains on the market even after FDA has been alerted. To the extent that unlawful diagnostics are aggressively promoted, it can discourage IVD manufacturers from making the investments necessary to obtain FDA approval or clearance.

Conclusion

Other steps can also be taken to facilitate the FDA review process and make it more attractive. This article is hardly an exhaustive list. For example, OIVD is looking at electronic submissions. OIVD has already taken many positive steps, such as holding pre-IDE meetings, providing rapid feedback via e-mail to facilitate communications, and showing flexibility, such as its use of the de novo process. However, it is important that FDA, the IVD industry, laboratories, and other stakeholders candidly critique the current review process and identify steps that will facilitate the product development, review, and approval processes for diagnostics. Clearer, more predictable, more transparent, and less regulatory pathways to market need to be available for IVD manufacturers that wish to introduce new types of diagnostic products. The atrophy of the statutory product development protocol mechanism illustrates what happens to a regulatory process when it becomes too costly, prolonged, cumbersome, and uncertain.

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