'If pharmacogenomics lives up to its potential the number of laboratories performing genetic-based testing will surely grow.'

editorial

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Pharmacogenomics: an in-house advantage?

The growing interest in pharmacogenomics and the recent solicitation of pharmacogenomic data by the FDA suggest that submissions of pharmacogenomic data for the regulatory approval of new drugs might become mandatory in the future. These data can be expected to form the basis of drug-labeling requirements that specify the approved patient population. To identify the appropriate patient populations, the FDA envisions the use of diagnostic test kits – also known as *in vitro* diagnostic devices (IVDs). Following this route will cause companies to bear additional costs and, perhaps, delays as companies seek regulatory approval for their IVDs and IVD manufacturing facilities. The genetic testing industry demonstrates that there is a more straightforward route for generating pharmacogenomic data – the in-house testing of patient samples; this is particularly appealing to small companies. In-house testing (as a service) is regulated by the Centers for Medicare and Medicaid Services (CMS), not the FDA. Additionally, in-house testing has several business advantages over the use of IVDs. This article examines the genetic testing industry and how the benefits of in-house testing could apply to the nascent pharmacogenomics industry.

The genetic testing industry is an apt subject for study because, similar to pharmacogenomic testing, it examines a patient's genome or gene products. However, whereas genetic testing frequently calculates the probabilities of developing a disease, pharmacogenomic studies help to determine the proper medicine to prescribe. Because the genetic testing industry provides information as a service, not products, it falls outside the FDA radar. Additionally, the genetic testing industry relies almost exclusively on in-house or 'home-brew' assays, which are designed, conducted and evaluated in-house using in-house or vendor-supplied components.

Regulatory structure

Like the FDA, the CMS is monitored by the Department of Health and Human Services (DHHS). The authority of the CMS to regulate genetic and other in-house testing service providers stems from the Clinical Laboratory Improvement Amendments (CLIA) act of 1988 [1]. The CMS requires that laboratory service providers register with the CLIA program and become certified*. Certification is usually provided by an entity that is recognized by an approved accreditation body and it ensures that the laboratories meet minimum quality levels, in terms of personnel qualifications, quality control procedures and proficiency testing programs [2]. The particular requirements for individual laboratory certification depend on the complexity of the tests employed [3]. CLIA has specific requirements for recognized specialty areas, such as cytogenetics and microbiology. It has not yet recognized genetic testing as a specialty area.

For certification, CLIA requires laboratories to demonstrate the analytical validity and reliability of their tests, but not their tests' clinical validity or utility [4]. This contrasts with the FDA requirements for IVDs, where all four properties must be demonstrated.

Under the Federal Food, Drug and Cosmetic Act (FDCA), as amended by the Medical Device Act (MDA) and Safe Medical Devices Act of 1990, the FDA claims regulatory oversight over all

*Washington and New York are exempt from the CLIA program because their state standards are more stringent.

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in-house tests and their components [5]. However, with the exception of analyte-specific reagents (ASRs), the FDA has chosen not to exercise its regulatory authority. A principle reason for the FDA's hesitancy is that the in-house testing process requires a physician's prescription and generates clinical information that is used for patient care decisions. As such, it occupies a gray area between medical devices and the practice of medicine, the latter being an area the FDA is not empowered to regulate [6].

ASRs became classified as medical devices in 1997 [7]. In effect, they are the active ingredients used in in-house tests and include antibodies, ligands and nucleic acids [8]. The FDA requires manufacturers of ASRs to register with the agency and to comply with labeling and good manufacturing practice (GMP) requirements [9]. Sales of ASRs are restricted to CLIA high-complexity certified laboratories. Laboratories that manufacture ASRs for internal use are, however, exempt from FDA regulations.

In contrast to in-house tests, IVDs are monitored under FDA regulatory authority. New IVDs are subject to FDA review by one of two methods. IVDs that are 'substantially equivalent' to already marketed IVDs can be submitted through the premarket notification [510(k)] process [10]. The average time required for approval following file submission was 100 days in 2002 (www.fda.gov/cdrh/annual/fy2002/ode/2002.pdf). Novel IVDs must be submitted for FDA review through the more arduous premarket approval (PMA) process [11]. PMA submission requires full reports of manufacturing quality control, nonclinical and clinical studies performed, and data to demonstrate clinical validity [12]. As expected, the time needed for approval via the PMA review process is longer (averaging 364 days in 2002).

CLIA regulations and the FDA drug approval process

In the future, the current CLIA regulations would only apply to the post drug-approval period, regarding pharmacogenomic-based medicine. They would not change a company's obligation to meet FDA requirements for the investigational new drug application (IND) process and the new drug application (NDA) process. Indeed, if the FDA allowed post drug-approval in-house testing, a company should expect to carry out testing to higher standards than required by CLIA. This would not be an unreasonable burden because the clinical validity and utility of the testing methodology would need to be established during normal drug development.

The principle problem envisioned for in-house testing is the need to overcome the expected opposition by the FDA to this testing approach. It is a concern that in-house testing is not mentioned in the FDA's recent guidance and concept papers on pharmacogenomic drug development (www.fda.gov/cber/gdlns/pharmdtasub.pdf, www.fda.gov/cder/genomics/pharmacoconceptfn.pdf).

A company proposing in-house testing would have the burden of convincing the FDA that they possess adequate expertise and resources to establish and maintain a testing facility. They might also have to propound their legal right to follow this testing approach. However, the rewards could justify the effort if the effort and expense of designing and testing an IVD (and then building a manufacturing facility) can be eliminated. For a small startup company, the potential savings in time and money could be crucial for success.

Changes in the regulatory wind?

Given the less stringent regulatory oversight by the CMS, one might suppose that efforts are underway within the DHHS to tighten up the supervision of the genetic testing industry. Yet, after four attempts to do this, starting in the late 1990s, action stalled in 2001 (interested readers can access the recommendations of the National Institutes of Health and the Department of Energy at www.genome.gov/10001733 and the Clinical Laboratory Improvement Act Committee's recommendations at www.phppo.cdc.gov/cliac/pdf/cliac598.pdf and the Secretary's Advisory Committee on Genetic Testing recommendations at www4.od.nih.gov/oba/sacgt.htm).

The FDA has so far avoided comment on the in-house testing industry and has made no move to acquire the regulatory supervision of the industry. Statutorily, as mentioned above, the FDA lacks the authority to regulate the practice of medicine. Additionally, the FDCA only empowers the FDA to regulate articles that move in interstate commerce, whereas the assays used for in-house testing are assembled on site. Institutionally, the FDA probably does not want to instigate a bureaucratic turf war with the CMS. The FDA might also recognize the sheer enormity of the task. Approximately 175,000 testing laboratories are covered by CLIA, of which an unknown number, possibly in the low thousands, are engaged in some form of genetic testing. If pharmacogenomics lives up to its potential the number of laboratories performing genetic-based testing will surely grow. It is, therefore, possible that the increased pressure that the review of pharmacogenomic data submissions would place on the FDA's institutional resources would be enough for the FDA to resist assuming another mission.

Business considerations of in-house testing

In-house testing could provide some significant business advantages because of the ability to maintain greater control over the testing process and the fact that a testing center can amass large quantities of clinical data. Reasons for this are:

1. Information (not products) is provided; a company would never face a product liability suit.
2. The use of a centralized testing facility provides an additional mechanism to ensure that only patients that meet strict patient selection criteria are allowed access to drugs with serious adverse drug reactions. This will be important when there is only one drug in the treatment class or when a company wants to reintroduce a withdrawn drug.
3. The use of a dedicated core facility increases the reliability and accuracy of test results.
4. The use of a centralized testing facility leads to better pricing control, preventing wholesalers from discounting tests, and also allows the establishment of a two-tier pricing structure for tests that can be used to predict disease disposition or to select therapy.
5. Capturing the testing service charges increases total revenue compared with IVD manufacturers.
6. In-house testing denies competitors access to a test. This could be particularly important if a company has a patent position that prevents a competitor from co-developing a competing test and drug. It might also impede medical researchers and competitors from developing off-label use of existing drugs that compete with a company's established products.
7. The use of a centralized testing facility allows proprietary knowledge and techniques to be protected as trade secrets.
8. In-house testing permits enormous amounts of clinical data to be collected, for example if a microarray composed of diverse genes is used. These data can be mined to examine new

relationships between disease states. If a microarray also includes genes used for patient selection regarding other drugs produced by the company then, if privacy concerns do not prohibit, the patient's healthcare provider (or perhaps the patient themselves) could be solicited to switch drugs.

A principle drawback of a centralized testing facility is that it cannot be used where disease management requires rapid intervention. Additionally, the market size for a particular test might require the establishment of satellite testing centers or partnering with other companies.

Conclusion

The regulatory, legal and business advantages of in-house testing could provide drug companies with a low cost and easier entry point into the pharmacogenomic market. The window is open for nimble companies; however, this might change as interest in pharmacogenomic based drugs grows, particularly if resolve builds within the DHHS to assert greater regulatory supervision over the in-house testing industry.

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