Pharmacogenomics

An In-House Advantage?

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With the expectation that future drug approvals may hinge on pharmacogenomic testing of patients, what are the advantages of the in-house testing of patient samples compared to supplying diagnostic kits? The genetic testing industry provides an interesting reference from which to examine this question. The genetic testing industry falls chiefly under the less stringent regulatory oversight of the Centers for Medicare and Medicaid Services (CMS), and not the Food and Drug Administration (FDA). Genetic testing is also a service and not a product, with different (perhaps lesser) legal liabilities. Additionally, in-house testing may provide unique business advantages. This article examines the genetic testing industry, and how the benefits of in-house testing may apply to the nascent pharmacogenomics industry.

Genetic and pharmacogenomic testing examine in essence the same thing: a patient’s genome or gene products, in order to predict an outcome. For genetic testing, the outcome may be the calculation of a lifetime risk of developing breast and ovarian cancer for siblings of patients that have mutations in the BRCA1 and BRCA2 genes. For pharmacogenomics, it may be the determination of the proper medicine to prescribe after examining the patient’s cytochrome P450 genes which encode a family of drug-metabolizing enzymes.

Regulatory Oversight

Within the Department of Health and Human Services (DHHS), there are two primary agencies with regulatory oversight of genetic testing. They are CMS, which oversees genetic testing service providers, and FDA, which oversees in vitro diagnostic devices (IVDs).

CMS regulates genetic testing service providers through the Clinical Laboratory Improvement Amendments of 1988 (CLIA). These service providers develop and use their own in-house or “home brew” assays. CMS requires that the service providers register with the CLIA program and become certified. Certification ensures that the laboratories meet minimum quality levels in terms of personnel qualifications, quality control procedures, and proficiency testing programs. Certification is usually provided by an entity recognized by an approved accreditation body. The regulatory requirements for certification depend on the complexity of the tests employed. The CLIA has specific requirements for recognized specialty areas such as cytogenetics and microbiology, but it has not yet recognized biochemical and molecular genetics as specialties.
The CLIA requires laboratories offering a test to demonstrate analytical validity and reliability, but not clinical validity or utility. Interestingly, CLIA does not require Institutional Review Board (IRB) approval when developing new testing programs that do not rely on human subjects or receive federal funding.

FDA has regulatory oversight over all laboratory tests and their components under the Federal Food, Drug and Cosmetic Act (FDCA), as amended by the Medical Device Act and Safe Medical Devices Act of 1990 (MDA). FDA has, but for one exception, chosen not to exercise its regulatory authority over in-house testing. This hesitation may stem from the fact that genetic testing services are in a gray area between medical devices and medical procedures, the latter being an area FDA is not empowered to regulate.

In 1997, FDA classified analyte specific reagents (ASRs) as medical devices[8]. These reagents are in effect the active ingredients used in the in-house tests and include antibodies, ligands, and nucleic acid sequences. FDA requires manufacturers of ASRs to register with the agency and to comply with labeling and good manufacturing practices (GMP) requirements. Sales of ASRs are restricted to CLIA high-complexity certified laboratories. Laboratories that manufacture ASRs for internal use are exempt from FDA regulations.

FDA regulates diagnostic genetic test kits IVDs. The approval of new IVDs that are “substantially equivalent” to marketed IVDs can be achieved through the 510(k) process. Novel IVDs must be submitted through the more arduous premarket approval (PMA) process. PMA submission requires full reports of nonclinical and clinical studies performed for the product, manufacturing quality control mechanisms, and data to demonstrate clinical validity.

How Do the CLIA Regulations Affect FDA Drug Approval Process?

CLIA regulations should not affect the review process, as they cover post-approval testing of patient samples. Neither Guidance for Industry Pharmacogenomic Data Submissions (available at http://www.fda.gov/cber/gdlns/pharmdtasub.pdf) nor Drug-Diagnostic Co-Development Concept Paper (available at http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf) addresses this issue. Even though CLIA regulations do not require proof of clinical utility or validity, these data will be required by the FDA. More specifically, Guidance for Industry states that pharmacogenomic data submissions for investigational new drug applications (INDs) will be required if the results: (1) affect the design of specific animal safety trials, or human safety or efficacy trials; (2) are used to support scientific arguments; or (3) constitute a known valid biomarker. For new drug applications (NDAs) and biologics license applications (BLAs), pharmacogenomic test results will be required if the data is to be included in the drug label or as part of the scientific database being used to support approval.

The use of CLIA may, however, speed up and reduce the uncertainty of the review process. In-house testing eliminates the additional need and expenses of designing an IVD, building a manufacturing facility, and getting both of these approved. For a small startup, the savings in time and money may make the difference between a successful, independent company and an insolvent one.
Changes in the Regulatory Wind?

Attempts by CMS and HHS to increase regulatory oversight of genetic testing have stalled. Two committees released reports in the late 1990s recommending an increased oversight of genetic testing laboratories (The National Institutes of Health and the Department of Energy’s report are available at http://www.genome.gov/10001733 and the Clinical Laboratory Improvement Act Committee’s report summary is available at http://www.phppo.cdc.gov/cliac/pdi/cliac598.pdf). These were followed in 2000 by an issuance of a Notice of Intent that HHS would prepare a notice of proposed rulemaking (NPRM) regarding the creation of a genetic testing specialty under CLIA. The same year, HHS chartered the Secretary’s Advisory Committee on Genetic Testing (SACGT) to convene a working group to discuss a methodology of classification of genetic tests, in the hope that this would provide regulatory agencies with more appropriate tools to evaluate and regulate the industry (The Development of a Classification Methodology for Genetic Tests: Conclusions and Recommendations of the Secretary’s Advisory Committee on Genetic Testing, September 2001, is available at http://www4.od.nih.gov/oba/sacgt.html). Public comment on SACGT’s proposal resulted in SACGT tabling the matter.

FDA has not taken further action regarding in-house testing. It did release, in 2003, Analyte Specific Reagents: Small Entity Compliance Guidance; Guidance for Industry (available at http://www.fda.gov/cdrh/oivd/guidance/1205.pdf), but this report just summarizes the existing regulations.

Besides questionable regulatory authority, FDA’s hesitancy may also stem from the enormity of the task. Approximately 175000 testing laboratories are covered by CLIA, of which an unknown number, possibly in the low thousands, engage in some form of genetic testing. If pharmacogenomics lives up to its potential, the number of laboratories will surely grow. The increased strain that pharmacogenomic data submissions would place on the FDA’s institutional resources may be enough for it to resist assuming another mission.

Different Legal Liabilities

The chief difference between testing services and diagnostic kit manufacturers is that testing services provide information and therefore do not face the prospect of product liability lawsuits. Both, however, can be held liable for negligence if they do not exercise due care.

Negligence

To be liable, a plaintiff must establish the four standard tort elements: duty, breach, causation, and damage. Compliance with applicable safety regulations or laws is relevant in determining whether the duty of care was breached. If the regulations or laws were intended to prevent the kind of harm suffered, then noncompliance is usually sufficient for
a holding of negligence per se, unless the defendant can establish a justification or excuse. In contrast, compliance is relevant, but not dispositive, because a reasonable manufacturer may take additional precautions. Since genetic testing is not recognized as a specialty by the CLIA, only general good laboratory practice regulations are applicable. Therefore, a service provider should establish a strict set of internal standards and procedures to follow to provide more protection. While both industries create tests, in-house testing services may have more opportunities for negligent acts by virtue of the fact that they also conduct and analyze the tests.

Causality can be difficult to establish with genetic tests because there is often a long lag time between providing the information and the occurrence or non-occurrence of an event. On the other hand, proving causation for pharmacogenomics testing is easier because the information will most likely be acted upon immediately.

Product Liability

There are three recognized categories of product defects: manufacturing defects, design defects, and inadequate instructions or warnings.

Strict liability attaches for manufacturing defects. So, even if the manufacturer used reasonable care in making and testing the kit and complied with applicable regulations, it will still be held liable for any harm caused by the kit. Harm could arise, for example, from including deteriorated, mixed up, or wrongly labeled reagents in a kit that then led to an erroneous test result.

A doctrinal split exists for design defects. The minority of jurisdictions treats medical devices as prescription drugs and exempts the manufacturers from liability. The majority undertake a case-by-case determination of whether a design defect exists. The standard used asks whether “the foreseeable risks of harm posed by the product could have been reduced or avoided by the adoption of a reasonable alternative design . . . and whether the omission of the alternate design renders the product not reasonably safe.”

A diagnostic test could be viewed as defective if there are reasonable alternative designs that would have a lower error rate, higher specificity or sensitivity for the analyte, greater recognition of more pathogenic mutations in a gene for a particular disease, or reduced the chances of an interpretation error of the test results by the healthcare professional conducting the test.

Failure to adequately warn or instruct results in the primary basis for the liability of manufacturers of prescription drugs and medical devices. Manufacturers have traditionally been shielded from liability to patients because of the “learned intermediary rule,” which places the physician as the gatekeeper to access to the drugs or devices. The learned intermediary rule is, however, slowly being eroded by the pharmaceutical industry’s direct-to-consumer marketing that bypasses the physician-patient relationship.

Benefits of In-House Testing

In-house testing provides greater control in ensuring that only patients that meet strict patient criteria are prescribed a drug that has serious adverse drug reactions. This is important when there is only one drug in the treatment class or when a company wants to reintroduce a withdrawn drug. Restricted access to a drug through a testing
mechanism also prevents off-label drug use that could be detrimental to a company’s reputation.

The presence of a dedicated core facility with experienced personnel reduces operational errors, and when problems arise they can be quickly addressed.

Pricing structure can be better controlled through in-house testing. A two-tier pricing structure can be established for tests that can be used to both predict disease disposition and select appropriate therapy. A company could maximize its revenue by charging higher fees for predictive testing and for diagnostic testing which does not accompany a prescription. Bundling diagnostic testing with a prescription allows a company to charge a lower testing fee, the cost of which can be recouped over the duration of the prescription. For drugs used for chronic conditions, the testing service could be offered free-of-charge as a means of promoting the use of the drug. Similarly, providing free or low-cost testing might be a means of inducing a 3rd party payer to include the company’s drug in the payer’s approved formulary. For low-cost tests, a competitor’s patients could be offered free testing to determine whether they are more appropriate candidates for the company’s therapy.

In-house testing prevents the use of a test by a competitor. This may be particularly important when a company has a patent position that prevents a competitor from developing a competing test. Given the expected future request for pharmacogenomic data by the FDA in the review of drug applications, denying a simple means of patient testing could hamper a competitor’s development of “me too” and second-generation drugs. In-house testing could also impede medical researchers and competitors from developing off-label use of existing drugs that would compete with the company’s established products.

In-house testing allows proprietary knowledge and techniques to be protected as trade secrets.

Enormous amounts of clinical data can be collected, particularly if a microarray composed of a diverse collection of genes is used. This data can be used in several ways. The data could be mined to examine new relationships between disease states. If a microarray also includes the genes known to be involved in selecting patients for all the drugs produced by a company, and if privacy concerns do not prohibit, then the patient’s healthcare provider or perhaps the patient himself/herself could be solicited to switch drugs.

Disadvantages of In-House Testing

The turnaround time between sample submission and test results prevents the use of in-house testing for diseases that require rapid intervention.

Conclusion

The regulatory, legal, and business advantages of in-house testing services for drug companies may provide an easier, lower cost entry point into the pharmacogenomic market. The window is open for nimble companies, but change may come if considerable bureaucratic inertia can be overcome and turf wars avoided.