

Overcoming



Product Development



Challenges Through



Innovation and Regulation

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The cost of bringing a new drug to market has surpassed \$1 billion (US).¹ Simultaneously, pharmaceutical companies are facing budget constraints, empowered patients are demanding high-quality drugs, legislators are demanding increasing oversight to ensure patient safety, and pioneering scientific discoveries are evolving at a rapid pace.² Faced with increasing regulatory requirements regarding patient safety and the challenges of managing global clinical trials, what can the pharmaceutical industry do to improve the efficiency and cost-effectiveness of drug discovery and development? This article reviews the changing landscape in product development and the establishment of regulatory tools for evaluating product development. It addresses some recent scientific discoveries that can help produce safer, more-effective products, as well as US Food and Drug Administration (FDA) initiatives being implemented to enable greater patient safety.

The current drug development and approval system is outdated, inefficient and expensive. It frequently uses technological standards developed almost a half-century ago to evaluate drug candidates discovered using the latest advances in basic science. Meanwhile, pharmaceutical research and development expenditures have risen 250% in the last decade, but the number of innovative new therapies submitted for FDA approval declined by approximately 50% during the same time frame.³ These issues highlight the need for a more efficient critical path—the risky “path that a medical product takes, from development to mass-production and availability, to the public.”⁴

Whether producing devices, drugs or biologics, medical product developers must navigate three key scientific/technical elements on the road from scientific innovation to commercial production. These elements are: assessing safety, demonstrating medical benefit and commercial-scale product manufacturing. The uncertain period when a product moves from the preclinical stage into clinical trials must be modernized to quickly and effectively move medical discoveries from the laboratory to consumers.

Along with industry changes in pharmaceutical drug development, changes are needed in the regulatory evaluation and approval process, especially regarding patient safety. Launched in 2004, the Critical Path Initiative (CPI) is FDA’s effort to “stimulate and assist a national effort to modernize the scientific process—the Critical Path—through which FDA-regulated products are developed, evaluated and manufactured.”⁴ Another component of the plan to modernize the agency is the *Food*

and Drug Administration Amendments Act of 2007 (FDAAA). *FDAAA* gives FDA greater drug safety oversight authority and tools, including the ability to require labeling changes and Risk Evaluation and Mitigation Strategies (REMS).

There currently is a revolution in drug development to improve productivity and increase the efficiency of bringing drug candidates through the clinical trial process. Pharmacogenomics, good design controls, biomarkers, adaptive trials and Bayesian statistics are some of the instruments being incorporated by drug development companies to enable the paradigm shift in how product development is pursued.

Overcoming Drug Development Challenges—Scientific Advances

Pharmacogenomics

In short, pharmacogenomics (PGx) is the science of how an individual’s genetic makeup affects the body’s response, both pharmacokinetically and pharmacodynamically, to drugs. FDA defines pharmacogenomics, as related to drug response, as the study of variations of DNA and RNA characteristics, and further defines pharmacogenetics (PGt) as a subset of PGx that studies the variations in DNA sequence.⁵ To study PGx, one must have a biomarker and a tool to measure it (RxDx, discussed below). PGx is used during all phases of drug development to assess safety and efficacy, and its many benefits, as well as a few drawbacks, have been published (see **Table 1**).⁶ A study of patients hospitalized in 1994 reported that adverse drug reactions (ADRs) accounted for more than 2.2 million serious incidents and more than 100,000 deaths, making ADRs one of the leading causes of hospitalization and death in the US.⁷ PGx has the potential to dramatically reduce these numbers and may be the way to prevent many ADRs.

In fact, PGx is applied in clinical trials in a limited capacity today. Clinical trial researchers use genetic tests for variations in CYP genes, which encode liver metabolic enzymes, to screen and monitor patients. The AmpliChip CYP450 test analyzes two genes in the CYP family by identifying a patient’s genotype. Based upon this analysis, patients are assigned a predicted phenotype of poor, intermediate, extensive or ultrarapid metabolizer. This more-accurate system of determining an effective drug dose may enhance patient safety.

Patients are increasingly receiving PGx information as it becomes more prevalent. A current study indicates that nearly 25% of all outpatients now receive one or more drugs that



have pharmacogenomic information in the labeling.⁸ This emerging PGx technique shows great promise for contributing biomarkers to target responders and monitoring clinical response. As understanding grows that people and diseases differ at the genetic or molecular level, doctors will be able to tailor treatments to individual patients based upon a disorder's actual biology, not just according to symptoms. However, this technique must be further developed and standardized before it can be widely used.

Biomarkers

FDA defines a biomarker as, "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."⁹ In short, a biomarker is an indicator of a particular physiological state. Historically, biomarkers were physiological indicators such as respiration rate, blood pressure or heart rate. Recently however, the term biomarker has become synonymous with "molecular biomarker." Molecular biomarkers include elevated prostate-specific antigen for prostate cancer or, as mentioned, analyzing CYP family genes as a liver function test. Genomic biomarkers, more specific to individuals than molecular biomarkers, can play an important role in identifying responders and nonresponders, avoiding toxicity and modifying drug dosage to optimize safety and efficacy.

An exploratory biomarker is considered valid if it can be measured in a test system with well-established performance characteristics and if there is evidence of its clinical significance. Biomarkers are classified as either known valid, i.e., accepted by the scientific community to predict clinical outcome, or probable valid. Probable valid markers appear to have predictive value but have not yet been replicated or widely accepted. A biomarker's classification will lead to conditions for validation in the context of its proposed use. An FDA reference guide outlines the filing requirements for these data,¹⁰ and the agency's biomarker qualification pilot process is well under way.¹¹

A classic example of a known valid biomarker is Human Epidermal growth factor Receptor 2 (HER2/neu) overexpression. Patients overexpressing this biomarker are eligible for treatment with Herceptin (trastuzumab). When Genentech began selling Herceptin along with a diagnostic test to determine a patient's HER2 status, it heralded a future where medical treatment could be customized to an individual patient's genetic profile. Challenges specific to the development of

drug-test (RxDx) combination/companion products consequently emerged.

Drug-Test Combination Diagnostics—RxDx

RxDx combination products pair a drug and a diagnostic test that help physicians make better decisions about how to use the drug in question by identifying which patients will most likely benefit from treatment.

Two categories of these products exist. The first is a test developed after a drug is on the market. An example is the Vitamin K Epoxide Reductase Complex test that helps determine an individual's Coumadin starting dose. The second is a test developed in combination with a drug and required for the use of that drug, the companion diagnostic test. Examples include the HercepTest, discussed above, used to help evaluate patients for whom Herceptin treatment is being considered, and the EGFR pharmDx kit, which helps identify colorectal cancer patients eligible for treatment with Erbitux.

Another approach is to use multiple indicators of biological function as a prognosis of disease. An example is the In Vitro Diagnostic Multivariate Index Assay (IVDMIA). Three criteria distinguish IVDMIA from other laboratory-developed tests: the use of clinical data, application of an algorithm and a result that requires the test developer's help to interpret. FDA released a draft guidance explaining the regulations regarding analyte specific reagent (ASR) production and marketing.¹² In this guidance, FDA acknowledged that it was not regulating IVDMIA through other means. The agency "believed it was regulating the primary ingredients of most in-house tests because it was regulating the common elements of in-house tests, including most ASRs, general purpose reagents, general purpose laboratory equipment, other laboratory instrumentation and control... IVDMIA include elements ... that are not among these primary ingredients of in-house tests and that, therefore, raise safety and effectiveness concerns." Existing IVDMIA have been regulated under an assortment of requirements, including the *Clinical Laboratory Improvement Amendments (CLIA)*, state regulations and other accrediting organizations. The molecular diagnostic microarray-based test, MammaPrint, is the first test to be cleared as an IVDMIA.

The benefits of RxDx companion products could be tremendous for both patients and society. The technology now exists to use the information in the human genome to make improved

Table 1. Benefits and Disadvantages of Pharmacogenomics

Improvements in the Drug Development Process	
Progress in drug discovery and approval processes	➤ Discovery of potential therapies will become progressively less complicated using genome targets.
	➤ Previously stalled drug candidates may be pulled off the shelf as they are linked to the genetic population they treat.
	➤ Clinical trial costs and risks will be diminished by targeting only a precise population whose appropriate genetic profile allows a reaction to a drug.
	➤ Drug approval times should decrease.
Net decrease in overall healthcare costs	➤ Number of failed drug trials should decrease with the use of personalized medicine.
	➤ Number of medications patients must try to find an efficient therapy and the time these patients are on medication would decrease.
	➤ Total number of adverse drug reactions would decrease.
Manufacture of more-substantial medicines	➤ Pharmaceutical firms will be able to create drugs based upon the molecules associated with genes and diseases. This can facilitate drug discovery and permit the production of robust therapies targeted to particular diseases.
Improvements in Public Safety	
Advanced testing for diseases	➤ Prior knowledge of an individual's disease susceptibility permits preventative monitoring and lifestyle changes and the introduction of treatments at appropriate times.
More-precise system of determining correct drug dosages	➤ Method of basing dosages on weight and age will be replaced by dosages based upon a person's genetics and metabolism, therefore maximizing the therapy's usefulness and decreasing the possibility of overdose.
Manufacture of better and safer drugs	➤ Doctors will analyze a patient's genetic profile and prescribe the best available drug therapy, taking the guesswork out of finding the right drug and dose, accelerating recovery time and increasing safety as the prospect of adverse reactions is removed.
Disadvantages	
Difficulty discovering gene variations involved in drug response	➤ Variations in the human genome sequence must be identified and analyzed to determine their involvement (if any) in a particular drug response. Realizing the impact of these gene variations is highly time-consuming and difficult.
	➤ Limited knowledge about which genes are involved with what drug response; it is likely many genes will elicit a single response.
Obstacles for drug companies to manufacture a large number of pharmacogenomic products	➤ Pharmaceutical companies are accustomed to developing drugs using a "one size fits all" system. Will they be willing to develop alternative drugs that serve only a small portion of the population if it costs \$1 billion (US) to bring a drug to market?
Difficulty in informing healthcare providers	➤ Introducing numerous pharmacogenomic products to treat one condition in different subsets of the population will cause difficulties to those prescribing and dispensing drugs.
	➤ Physicians must perform an extra diagnostic test to determine which drug is appropriate for each patient.
	➤ All prescribing physicians will need an enhanced understanding of genetics to ensure patient safety.



medicines that treat not just significant patient populations via the “one size fits all” approach, but also the individual patient through personalized medicine. However, current statistical evaluation for drug approval is based upon benefit relative to a control group. If this standard were to change, an existing or co-developed test would be required prior to clinical evaluation. At times, this paradigm will be impossible. A few biomarkers are known and have been used successfully in clinical trials. But, frequently, the science behind the marker is not sufficiently understood to co-develop a test. Additionally, decisions in the pharmaceutical and diagnostics industries are based upon economics. FDA may try to promote development of Rx Dx companion diagnostic products; however, manufacturers will be slow to develop these products due to the absence of an apparent economic gain.¹³ Which FDA center or division will be responsible for the review of the product? What incentives will be considered to promote development of these products and what will be the development costs? Can the cost of production be decreased over time? Some of these issues are addressed through recent regulatory advances.

Overcoming Drug Development Challenges—Regulatory Advances

Drug development process improvement must be enabled by changes in product approval paradigms, in addition to innovations at the bench. FDA’s Critical Path Initiative is intended to catalyze the use of new drug development technologies. The CPI focuses on ensuring patient safety via tools such as REMS and the model-derived standard for the exchange of FDA-regulated product information, including labeling content and coded information from labeling content (Structured Product Labeling—Physicians Labeling Rule, SPL/PLR). FDA also promotes collaboration with other regulatory agencies, industry, academia and community-based researchers to advance and promote personalized medicine and develop new ways to evaluate drugs during and after the development process. The agency has enabled collaborations through the Interdisciplinary Pharmacogenomics Review Group (IPRG), which advises and educates reviewers on utilizing pharmacogenomics in drug development. FDA has also facilitated biomarker validation through the IPRG, which develops frameworks for qualifying and validating biomarkers, and the Predictive Safety Testing Consortium (PTSC), which evaluates safety and toxicity data earlier in the drug development process.

Several guidance documents have been

published to help incorporate PGx into regulatory reviews and clinical practice, including:

- *Draft Companion Guidance to the Pharmacogenomics Guidance on Recommendation for the Generation and Submission of Genomic Data*¹⁴
- *Guiding Principles for Joint FDA EMEA Voluntary Genomic Data Submission Briefing Meetings*¹⁵
- “Table of Valid Genomic Biomarkers in Drug Labels”¹⁶
- *Laboratory Medicine Practice Guidelines and Recommendations for Analysis and Application of Pharmacogenetics to Clinical Practice*
- Part 2 of the Microarray Quality Control Initiative to identify sources of variability in genomic classifiers that may be derived from microarray gene expression and genome-wide association studies

As a corollary to the PGx guidances, the IVDMA guidance was also released, keeping the scope of PGx in mind.¹⁷

The CPI is based upon the premise that changes in regulations may potentially stimulate the translation of science to the clinic and ultimately to the market. The initiative continues to lay the groundwork for enabling standards and methods in a number of key areas. It is hoped this will catalyze the development of pharmaceuticals that are safer for each individual. For example, the CPI drove the relabeling of Warfarin to recommend testing of genetic variants prior to determining a dose. In parallel, the first Warfarin sensitivity test was approved to detect these genetic variants, and dosing models are being established to bring about safer initial dosing. These are unprecedented regulatory agendas.

Recently, nephrotoxicity biomarkers were submitted to PTSC for qualification through a pilot process. The resulting evaluation will lead to evidentiary standards and metrics for novel biomarker qualification.¹⁸ These biomarker data will be used with blood urea nitrogen and serum creatinine test results to evaluate renal damage and provide information about drug-induced renal toxicity. Although collecting data using the new tests is voluntary, if collected, they must be submitted. This is a big step in determining what will be required to qualify novel biomarkers. Until now, this uncertainty has made pharmaceutical companies reluctant to pursue the clinical applicability of novel biomarkers.

Janet Woodcock, MD, director of FDA’s

Center for Drug Evaluation and Research, stated “The development of these and other biomarkers can result in important tools for better understanding the safety profile of new drugs. We hope these biomarkers will lead to human tests that detect drug-induced kidney injury in people earlier than is now possible, and help healthcare professionals better manage potential kidney damage from drugs.”¹⁸ These biomarker-driven tests could lead to approved treatments for diseases where renal toxicity prevents the use of experimental drugs. With these sensitive tests, FDA could approve drugs for testing because patients could be monitored and the study halted at the first signs of renal toxicity.

Changes in the landscape of product development have arrived as seen with Erbitux, Herceptin, Gleevec, Iressa, Tarceva, Nolvadex and others. Other impending changes, requiring personalized response data and the extent of genetic information included in the label, are apparent in the Warfarin dosing study.

Overcoming Device Development Challenges

With the need for co-developed diagnostics and/or devices to administer personalized treatment, companies cannot afford to release unsafe or ineffective products. Quality by Design (QbD) is defined as “designing and developing a product and associated manufacturing processes that will be used during product development to ensure that the product consistently attains a predefined quality at the end of the manufacturing process.”¹⁹ This is another regulatory effort to enable safe device production and use.

According to Woodcock, “Good pharmaceutical quality represents an acceptably low risk of failing to achieve the desired clinical attributes. QbD means that product and process performance characteristics are scientifically designed to meet specific objectives, not merely empirically derived from performance of test batches.”²⁰

To achieve QbD objectives, preferred product and process performance attributes must result from a combination of prior knowledge and experimental assessments throughout product development. This combination of data allows construction of a multivariate model relating product and process measurements and desired attributes.²⁰ A clinical study then is conducted to confirm the performance analysis.

The final connection between the product and the customer-driven quality attributes is the manufacturing quality system. Ideally, the quality

system reflects and addresses customer requirements, ensures integration of product and process knowledge gained during development, ensures ongoing control of manufacturing processes and enables continuous improvement.²²

Among the design features and decisions eliciting a high degree of confidence that manufactured lots will have the proposed product quality and performance are:

- designing to specifications and not setting specifications retrospectively
- instead of testing to document quality, establishing redundant end product testing to add an extra layer of security
- justifying established design features and describing why they deliver the proposed quality with certainty

Addressing the 2008 Parenteral Drug Association (PDA)/FDA Joint Regulatory Conference on 8 September 2008, Woodcock stated, “Nobody... wants poor-quality [products] out on the market... so it is key [to] push regulatory harmonization.”²¹ While there is a need to take action when quality is poor, continuous improvement must be facilitated. Toward this end, FDA is continuing the Pharmaceutical GMPs for the 21st Century initiative. Under this initiative, the agency acknowledged that some of its previous GMP approaches and methods were “too repressive... taking responsibility for quality and stifling continuous improvement. Regulators [must] facilitate change and improvement, but at the same time... make sure that quality is maintained.”²¹ FDA has also increased its international outreach via the Beyond our Borders initiative, staffing liaison offices around the world, most recently in China and India.

As recent scientific breakthroughs demonstrate, “humankind reveals a penchant to pioneer first and plan later. It is a simple truth that technology develops faster and further than policy.”²² As genetic information becomes publicly available, policies and a regulatory framework for ethical, legal and social issues will be required. The first step in protecting against genetic discrimination, the *Genetic Information Nondiscrimination Act*, was passed in April 2008. This bill, called “the first civil rights bill of the new century of life sciences,”²³ prohibits health insurers from asking for, or using, genetic information to make a decision about coverage or to set premiums. However, the bill’s scope does not take into account other forms of insurance coverage, such as life or long-term care. Policies need



to be established for genetic testing of children to identify prognostic markers, reimbursement for pharmacogenomic testing in general, patients identified with prognostic disease markers and for issues yet to be identified as PGx becomes second nature in drug development and clinical practice. Education on PGx and biomarkers is currently lacking for the patient, payer and provider.

With new tools pushing drug development limits, it is hoped that scientific advances will eventually enable pharmaceutical companies to use genomic screening techniques linked to biomarkers early enough in the development process to identify drugs that are likely to cause serious side effects in a substantial portion of the treatment population. The need to co-develop a diagnostic and pharmacogenomic product will pose problems due to the inherent differences between the drug and diagnostic sectors.¹¹

Will scientific innovations and the regulatory advances to support them increase the threshold for what qualifies as a safe drug? Will the new paradigm increase the costs of discovering and validating unknown biomarkers? How much will it cost to align manufacturing operations with QbD? Will the need for additional clinical studies to validate a PGx marker, and studies prospectively designed and randomized by genotype, drastically increase clinical trial costs? How will these development costs impact the final cost of marketed drug-diagnostic combination products? In the end, patient safety is paramount, and all players must ensure patient safety comes first.

Conclusion

One aspect of the existing drug development process is the lack of understanding of a disease. This aspect may be addressed by changes in the product development landscape. Partnerships are essential to share and clinically qualify biomarkers cooperatively between academia, industry and government. Data integration and sharing are necessary to create a comprehensive disease evolution model that includes biomarkers and pharmacogenomic information able to identify patient populations. This paradigm shift will require more coordination between the FDA centers within the agency to promote co-development of drugs and diagnostics. Regulatory tools, including REMS and the CPI, are also being created to assess these product development challenges. Additionally, agency initiatives, including FDAAA and QbD, are being implemented. The impact of these initiatives is yet to be seen. ■

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