

SPECIALTY PHARMA

Strategies For Business Development

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James N. Czaban is a Shareholder in the Washington, DC, office of Heller Ehrman White & McAuliffe, where he leads the FDA Practice Group. Jim has more than 12 years experience in FDA regulatory and legal matters, and represents both specialty and large pharmaceutical and biotechnology companies in matters involving the regulation of drugs and biologics. His work encompasses all stages of a product's lifecycle, including pre-clinical research, development of appropriate clinical stage regulatory strategies (including the effective use of meetings with FDA), drafting and negotiation of marketing applications (NDAs, 505(b)(2) NDAs, BLAs, ANDAs, Rx to OTC switches), post-approval promotional compliance (DDMAC advertising oversight, Medicare/Medicaid reimbursement, fraud, abuse, and anti-kickback), and Hatch-Waxman/lifecycle management issues. He also regularly advises clients on licensing agreements (for products and patents), mergers, acquisitions, and other business transactions involving FDA-regulated products and entities, and frequently represents clients in contested administrative proceedings (Citizen Petitions and private negotiations with FDA), as well as FDA-related lawsuits arising under the Administrative Procedure Act and the patent laws. Jim has contributed to three legal treatises, written numerous articles, and lectured extensively at law school and industry courses on Food & Drug law. He has also been named one of Washington DC's "Top Lawyers" in Food & Drug Law by Washingtonian Magazine.

Emerging Regulatory Developments in Pharmacogenomics

By: James N. Czaban, Esq., Heller Ehrman LLP

Introduction

It has been several years since the announcement, with great fanfare, that the human genome had been mapped. Many saw this scientific milestone as the opening of the pharmacogenomic era, in which specialized pharmaceutical research would lead rapidly to widespread development of "personalized medicine" — drugs and biologics narrowly tailored to individuals' specific genetic variations. Although the early scientific and market hopes have proven unrealistic in terms of timing, the FDA has recently issued a final Guidance on the use and submission of pharmacogenomic data in drug and biologic product applications that provides reason to believe that new therapies finally may be making their way through the regulatory approval process in the not-too-distant future. As this field of research offers potentially innumerable opportunities for Specialty Pharma companies to develop unique and profitable products, careful attention to, and understanding of, the FDA's new Guidance is imperative.

What Is Pharmacogenomics?

Pharmacogenomics can be defined broadly as the application of genetic information to the development and use of therapeutic products. The FDA proffers a more specific definition for purposes of its Guidance, stating that pharmacogenomics means "the use of a pharmacogenomic or pharmacogenetic test in conjunction with drug therapy." Under any definition, pharmacogenomics is based on the fact that individuals exhibit genetic variations (besides the outwardly obvious physical differences) that can cause even seemingly similar individuals to respond quite differently to particular drugs, in terms of efficacy, safety, pharmacokinetic responses, or all of the aforementioned. Because drugs have traditionally been approved based on broad scale, genetically non-differentiated study populations, some drugs that show an appropriate balance of efficacy and safety in such groups may receive approval yet still be ineffective and/or unsafe in certain people.

The hope for pharmacogenomics is to be able to identify genetic variations that predict an individual's response to a particular therapeutic product to reduce risks and improve outcomes. The FDA's Guidance, while recognizing that "the field of pharmacogenomics is currently in early developmental stages and [that its] promise has not yet been realized," is the first significant regulatory step toward a system that encourages and facilitates the wider use of pharmacogenomic research and technology in the drug development and approval process. And, while the Guidance appears competition neutral, many of the recommendations and approaches outlined within will have an impact on how companies plan for and execute strategies to maximize the commercial value of their investigational drug products. Thus, aside from the societal medical benefits of pursuing pharmacogenomics in drug development, such approaches will have an appreciable impact on Specialty Pharma companies' bottom lines.

The Guidance

As the FDA notes, the Guidance is "intended to facilitate scientific progress in the field of pharmacogenomics to facilitate the use of pharmacogenomic data in drug development."

The Guidance provides specific recommendations, with examples, on (1) when to submit pharmacogenomic data to the FDA; (2) potential formats and content parameters for submission of such data; and (3) when and how the FDA will use such data in regulatory decision-making. The Guidance also specifies when pharmacogenomic data submission will be required, and when it may be made voluntarily.

Voluntary Genomic Data Submissions (VGDS)

The FDA's Guidance notes that currently, "most pharmacogenomic data are of an exploratory or research nature, and the FDA regulations do not require that these data be submitted to an IND, or that complete reports be submitted to an NDA or BLA." Nevertheless, the FDA emphasizes that voluntary submission of pharmacogenomic data can benefit the FDA and industry generally by educating and preparing companies and the FDA staff to handle future, more focused, pharmacogenomic submissions, and to avoid unnecessary delays in FDA review of future applications. Thus, the FDA is specifically encouraging companies to voluntarily submit exploratory pharmacogenomic data on drugs or drug candidates "whether or not the molecules are currently the subject of an active IND, NDA, or BLA." Such data may arise, for example, from microarray expression profiling studies, genotyping or single-nucleotide polymorphism (SNP) profiling experiments, or other emerging methodologies for analyzing gene functions generally.

According to the FDA, companies that submit voluntary pharmacogenomic data may realize the following benefits:

- Opportunities to meet informally with the FDA and to receive its expert assessment of specific data;
- The ability to participate in the evolving regulatory development process;
- Educating FDA officials at an early stage regarding novel pharmacogenomic experiments and the appropriate analysis and interpretation of data from such experiments;
- Receiving FDA feedback that can reduce agency review time later in a product's development cycle; and
- Obtaining FDA suggestions for new opportunities to develop previously shelved drug candidates using pharmacogenomic technology.

In preparation for VGDSs, the FDA has established a cross-center agency team, the Interdisciplinary Pharmacogenomic Review Group (IPRG) to develop policy and advise review divisions on the interpretation and evaluation of pharmacogenomic data. Although it has described several potential formats for VGDSs, the Guidance emphasizes the FDA wants to minimize the burden of VGDSs, and thus, has decided not to recommend any specific format for such voluntary submissions.

From a legal/regulatory perspective, pharmacogenomic data that falls within the voluntary submission categories should have no direct impact on review or approval of specific drug or biologic applications. However, it will be important for companies to accurately assess the nature and type of pharmacogenomic data considered for submission because the distinctions between voluntary data, and data the FDA will actually consider to be mandatory can be blurry.

Mandatory Submission of Pharmacogenomic Data

The FDA's Guidance discusses various scenarios under which pharmacogenomic data submission may be mandatory, either as part of an IND, a pending NDA/BLA, or as a supplement to an approved NDA/BLA, but the basic rule of thumb is that such submissions may be mandatory if the data will potentially serve as a basis for regulatory decision-making. A key "regulatory decision-making" scenario is where the data may support specific labeling statements for the approved drug. The FDA describes two such situations: (1) the pharmacogenomic data may be intended to be included in the drug labeling in a general informational manner; and (2) the pharmacogenomic data may be included in the drug labeling to choose a dose or dosing schedule, to identify patients at risk, or to identify patient responders (and non-responders).

“Known Valid” & “Probable Valid”

Pharmacogenomic Biomarkers:

As a general matter, the FDA’s mandatory submission guidelines also focus on whether the data at issue is derived from “known valid” or “probable valid” pharmacogenomic biomarkers. As the FDA acknowledges, currently most pharmacogenomic measurements are not considered valid biomarkers, but “certain markers (i.e., for drug metabolism) are well-established biomarkers with clear clinical significance.” Generally speaking, the regulatory decision-making criteria for mandatory submission will be based on whether the data represents known valid or probable valid biomarkers. According to the Guidance, a biomarker may be deemed to be a “known valid” biomarker if (1) “it is measured in an analytical test system with well-established performance characteristics and (2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results.” “Probable valid biomarkers” are described as those “that appear to have predictive value for clinical outcomes, but may not yet be widely accepted or independently verified by other investigators or institutions.”

Informational Pharmacogenomic Labeling

General informational labeling regarding pharmacogenomic factors in the use of a drug are expected to alert practitioners of the potential for dose adjustment or the possibility of heightened side-effect frequency or severity in patients with particular genetic variations, but without identifying that any specific genetic testing be conducted. This approach is anticipated when an FDA-approved genetic test is not available, or when approved tests are not widely available. In these circumstances, the Guidance urges proactive consultation with the appropriate review division (with potential participation by the CDRH’s Office of In Vitro Diagnostics, and other relevant CDER and CBER review divisions) in order to reach agreement on what the FDA considers to be potentially complex labeling and approval decisions.

Use-Specific Pharmacogenomic Labeling

For some drugs, the FDA expects to require specific pharmacogenomic labeling to guide the clinical use of the drug in appropriate patient populations. For example, labeling may require patients to be tested for drug metabolism genotype and dosed according to the test results. In other cases, labeling may instruct as to the selection of potential responders based upon genotype (of the patient herself, or of the patient’s tumor), or upon the gene expression profile. In a third set of cases, labeling may exclude certain patients based on genotype or gene expression profile, especially if such patients were excluded from the drug’s pivotal trials supporting approval.

Importantly, in all of the above situations, the FDA will recommend co-development of the drug and the appropriate pharmacogenomic test(s), if such tests are not already available. The FDA intends to issue future guidance on the co-development of drugs and associated pharmacogenomic tests, but current guidance from the Office of Combination Products may provide some insights into the complex regulatory issues involved in developing combination products.

Although the possibility of mandatory pharmacogenomic data submission poses a risk of extending and complicating the FDA’s drug review process (marketed products could face labeling changes), in many cases, this is not necessarily a reason to shy away from pharmacogenomic studies and research. Rather, sponsors should, in many cases, embrace the potential for mandatory submissions because ultimate inclusion of proprietary pharmacogenomic data in a drug’s labeling can serve as a point of market differentiation as well as the basis for added market exclusivity. Specifically, new product approvals, and labeling changes to previously approved products, may be eligible for a 3-year regulatory exclusivity period that bars approval of competing (generic) products for the same conditions of approval, if the labeling changes were the result of new clinical studies conducted by (or for) the applicant and those studies are deemed by FDA to be “essential to approval” of the labeling change.

Pharmacogenomic Data Submission Algorithms

Although the Guidance is not officially binding on applicants and sponsors, the FDA lays out a rationale for how it may require submission of pharmacogenomic data under the authority of existing regulations. The Guidance provides separate algorithms for the IND, new NDA/BLA, and approved NDA/BLA phases.

Submission of Pharmacogenomic Data During the IND Phase

The Guidance notes that current IND regulations, 21 C.F.R. § 312.23(a)(8), require the submission of “adequate information about pharmacologic and toxicological studies of the drug involving laboratory animals or *in vitro*, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed [human] clinical investigations.” From this, the agency concludes that “pharmacogenomic data relevant to, or derived from, animal or *in vitro* studies must ordinarily be submitted [in an IND] when the sponsor wishes to use those data to make a scientific case, or when the pharmacogenomic test is a known valid biomarker.” Similarly, based upon the requirements of sections 312.23(a)(9)-(11), the FDA concludes that sponsors must submit pharmacogenomic data that is of known or probable relevance (known valid pharmacogenomic biomarkers, or probable valid biomarkers) because such information

could aid in the FDA's evaluation of the safety of the proposed human clinical studies of the drug and/or in assessing the drug's mechanism of action. As FDA summarizes these mandatory IND submission requirements, pharmacogenomic data must be submitted if any of the following apply:

1. "The test results are used for making decisions pertaining to a specific clinical trial, or in an animal trial used to support safety (i.e., the results will affect dose and dose schedule selection, entry criteria into a clinical trial safety monitoring, or subject stratification)."
2. "A sponsor is using the test results to support scientific arguments pertaining to, for example, the pharmacologic mechanism of action, the selection of drug dosing and dosing schedule, or the safety and effectiveness of a drug."
3. "Test results constitute a known valid biomarker for physiologic, pathophysiologic, pharmacologic, toxicologic, or clinical states or outcomes in humans, or the test is a known valid biomarker for a safety outcome in animal studies."

The FDA will consider two pharmacogenomic submission scenarios to be voluntary if:

1. "Information is from exploratory studies or is research data, such as from gene expression analysis in cells/animals/humans, or single-nucleotide polymorphism (SNP) analysis of trial participants."
2. "Information consists of results from test systems where the validity of the biomarker is not established."

Submission of Pharmacogenomic Data During the New NDA/BLA Phase: As with the IND phase submission algorithm, the FDA bootstraps its existing NDA/BLA submission requirements into a de-facto pharmacogenomic data submission requirement under certain circumstances. Specifically, the Guidance identifies mandatory NDA/BLA submission situations to include those where the sponsor intends the pharmacogenomic data to be used in the product labeling or as part of the scientific database supporting approval, including data to support dose selection, assess safety, select patients, monitor beneficial responses, and/or to support label descriptions of pharmacogenomic tests essential to safe and effective use (including dose selection) of the drug. Such data should be submitted in full reports to the NDA/BLA. Abbreviated pharmacogenomic data reports can be used where pharmacogenomic test results from known valid biomarkers are used, but not relied upon directly for approval nor proposed to be used in labeling, or where results from probable valid biomarkers are used indirectly in support of the FDA's overall review of the drug or biologic. The Guidance notes that reports are not required to be submitted for general exploratory research, such as broad gene expression screening or collection of sera or tissue samples, or where the tests are not known or are probable valid biomarkers.

Submission of Pharmacogenomic Data to a Previously Approved NDA/BLA: The FDA also points out that existing regulations governing submission of new scientific information to a previously approved NDA or BLA, 21 C.F.R. § 314.81(b)(2) and 21 C.F.R. § 601.12 apply with full force and effect with respect to non-clinical or clinical pharmacogenomic investigations using known or probable valid biomarkers. However, pharmacogenomic study results of other types are not required to be submitted nor do they meet the voluntary submission criteria, although the FDA will accept the voluntary submission of such data, as well as data from pharmacoepidemiologic and observational studies.

Summary

The FDA's pharmacogenomic Guidance is an important first step toward a coherent, evolutionary approach to regulation of pharmacogenomics in drug and biologics development, review, and approval. While the Guidance may have immediate impact on some sponsors who have been developing pharmacogenomic data in connection with specific investigational products, the full impact of the FDA's foray into pharmacogenomic regulation is yet to be felt by many companies. Importantly, the Guidance does not require any sponsor to proactively begin developing pharmacogenomic data for its investigational or approved products. That day may come, but will likely require a more formalized regulatory process whereby the FDA promulgates new regulations pursuant to notice-and-comment rule making. In any event, developing familiarity with the Guidance, and the FDA's developing attitudes toward pharmacogenomics, is an investment that no Specialty Pharma company can afford to avoid. n