Pharmacogenomics is a rapidly evolving science with the potential to revolutionize drug discovery and development. Although biopharmaceutical companies have been generating pharmacogenomic data for more than a decade, these data have generally not been shared with the US Food and Drug Administration because they do not clearly fit into a traditional regulatory submission package. In addition, many sponsors believe that the FDA will use exploratory pharmacogenomic data for regulatory decision making. These factors have hindered the exchange of information between sponsors and the FDA. To facilitate that exchange, the agency published a draft guidance in November 2003 regarding the submission of pharmacogenomic data to investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs). This guidance has been in development for several years, and a number of workshops and seminars have provided much input to the FDA for its creation. Submission of pharmacogenomic data to INDs, NDAs, and BLAs is an opportunity to advance new technologies and apply them to the development of new and improved drug and diagnostic products.

Pharmacogenomics and Drug Development
Pharmacogenomics involves the use of genome-wide analyses to identify genes with altered expression or activation as a result of exposure to a drug (see the Glossary and For Further Reading boxes). Pharmacogenomics can identify markers to aid drug development in four key areas:

- exposure
- efficacy
- stratification
- toxicity.

Markers of exposure can determine whether the desired target tissues of a subject have been exposed to a drug at physiological concentrations. Markers of efficacy can provide molecular evidence above and beyond traditional clinical endpoints. Stratification markers can identify a subset of patients who may uniquely benefit from a given therapy. Finally, toxicity markers can predict and prevent adverse events.

Draft FDA Guidance
Because the field of pharmacogenomics is relatively new, experimental results may not be well enough established to be suitable for regulatory decision making. The regulations relevant to drug safety and efficacy were developed before the widespread use of animal or human genetic or gene expression testing, and they do not address when such data should be submitted.

The FDA received inquiries about what the regulations require of sponsors who are conducting pharmacogenomics testing. In response to those queries, the agency published a draft guidance entitled Guidance for Industry: Pharmacogenomic Data Submissions. The guidance explains when sponsors should submit pharmacogenomic data to the FDA during drug development and review, what formats to use for submissions, and how the data might be used in regulatory decision making. This guidance interprets the regulations for IND, NDA, and BLA submissions and clarifies the agency’s thinking about when pharmacogenomic data must be submitted.
be submitted and when its submission is voluntary. It also clarifies how the FDA intends to use pharmacogenomic data in regulatory decision making (in other words, when pharmacogenomic data will be considered sufficiently robust to serve as a basis for regulatory decision making), when pharmacogenomic data will be considered supportive to a regulatory decision, and when pharmacogenomic data will not be used in regulatory decision making.

In general, exploratory pharmacogenomic data are not required submissions to INDs; however, the FDA encourages their inclusion in INDs as a voluntary genomic data submission (Figure 1). If such data are used by the sponsor for decision making in a clinical study or are used to support safety in an animal study, then the data should be submitted in a full report to the IND. If exploratory pharmacogenomic data are generated with a known biomarker, then the data should be submitted to the IND in an abbreviated report.

In general, exploratory pharmacogenomic data should be submitted to a new NDA or BLA in a synoptic report; however, the FDA encourages their inclusion in NDAs or BLAs as a full voluntary genomic data submission (Figure 2). If pharmacogenomic data are used for regulatory decision making (to support a label or approval), then they should be submitted as a full report to the NDA or BLA. If exploratory pharmacogenomic data are generated with a known biomarker, the data should be submitted to the NDA or BLA in an abbreviated report. For an approved NDA or BLA, pharmacogenomic data generated using valid biomarkers should be submitted in an abbreviated or synoptic report (Figure 3). Exploratory pharmacogenomic data are not required to be submitted to an NDA or BLA, but a full voluntary genomic data submission is encouraged.

In the guidance, the FDA states that data submitted voluntarily will not be used in regulatory decision making. Therefore, such data cannot support or hinder a sponsor’s IND, NDA, or BLA.

**Glossary**

**Biomarker:** a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

**Genomics:** genomewide analyses to identify genes or variations in genes with the potential for assigning function to a given gene or variation

**Pharmacogenomics:** use of genomics (microarray technology, for example) to identify one or more genes with altered expression or activation as a result of exposure to a given drug

**Pharmacogenetics:** study of how variation in a single gene or limited subset of genes leads to variation in action, absorption, or distribution of drugs

**Regulatory decision making:** decision by the FDA to determine approvability or appropriate use of a drug or diagnostic product

**Toxicogenomics:** assessment of alterations in gene expression that influence, predict, or define toxic effects of drugs

**Valid biomarker:** a biomarker measured in an analytical test system with well-established performance characteristics and an established body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results; a biomarker that is appropriate for regulatory decision making

**Effects of the Guidance on the FDA**

The FDA recognized the need for specialized expertise to review genomic data submissions. To address that need, the FDA created a cross-center Interdisciplinary Pharmacogenomics Review Group (IPRG) to review voluntary genomic data submissions, work on ongoing policy development, and advise review divisions on pharmacogenomic data. Voluntary genomic data submissions will be analyzed by the IPRG and the relevant review division staff. However, the reviewing division will not act on the voluntary data submission. A review division may also consult the IPRG when pharmacogenomic data are part of a required submission to an IND, NDA, or BLA. This process is intended to ensure that scientific
If after a voluntary genomic data submission additional data become available that make the pharmacogenomics data a required submission, the sponsor must amend the IND, NDA, or BLA. If the FDA becomes aware of the significance of a particular pharmacogenomics test after evaluating results across sponsors, the agency will notify those affected.

Industry Reaction to the Guidance

Sponsors remain confused about the requirements for voluntary and full genomic data submissions. For example, many are unclear how the predicate rules (GLP, GCP, and GMP regulations) will apply to pharmacogenomic data in nonclinical and clinical studies. Sponsors are uncertain how much data voluntary and/or full genomic data submissions should include: the data on all genes studied or just those on genes of interest? Some sponsors are also unclear about the level of validation needed to support a voluntary full genomic data submission.

Sponsors are apprehensive about the use of pharmacogenomic data in the review process. Questions to the FDA have reflected concern that the agency will raise new questions and require additional data based on findings from exploratory pharmacogenomics studies, that new studies will be required or suggested based on preliminary pharmacogenomic data, that indicated populations will be narrowed or restricted based on pharmacogenomic data in subgroups, or that new studies will be required after retrospective subgroup analysis. Sponsors involved in worldwide drug development are also questioning whether the FDA, EMEA, and other health authorities will view pharmacogenomic data differently from one another, and if so, how those different views will affect worldwide drug development, review, and approval processes. Sponsors have expressed concern about the effect of voluntary genomic data submission on intellectual property and the added costs of pharmacogenomics submissions to an already expensive drug development process. Perhaps the greatest apprehension from sponsors regards what will happen when new data reclassify a voluntary genomic data submission as a required submission.
Worth the Effort

Although the current drug development process is adequate without its use, the application of pharmacogenomics to drug discovery and development can positively affect public health by improving drug candidate selection, selecting out patients who might experience the greatest degree of drug toxicity, selecting in patients who might benefit most from a drug (those who might achieve highest efficacy), and rationalizing dose selection. The FDA has publicly stated that incorporation of pharmacogenomics into the drug development and review process is a major goal of its new strategic plan, and pharmacogenomics is clearly aligned with the agency’s mission to protect and enhance public health.

As such, the November 2003 draft guidance is intended to reduce uncertainty about and encourage the use of pharmacogenomics for and by sponsors. If the industry views this guidance as an opportunity instead of a liability and commits to working with the FDA on appropriate use of the data, we can together use pharmacogenomics to protect and enhance public health.

Donna Morgan Murray, PhD, is executive director of global regulatory science at Bristol-Myers Squibb Company, 5 Research Parkway Department 718 (3SIG-511), Wallingford, CT 06492, 1-203-677-3824, donna.murray@bms.com.