



Biotechnology Industry Organization  
1225 Eye Street NW, Suite 400  
Washington, D.C. 20006

February 2, 2004

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, Maryland 20852

Re: Docket No. 2003D-0497, Federal Register: November 4, 2003 (Volume 68, Number 213, Page 62461-62463)

Dear Sir/Madam:

The following comments are provided by the Biotechnology Industry Organization (BIO). BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations in all 50 U.S. states and 33 other nations. BIO members are involved in the research and development of health-care, agricultural, industrial and environmental biotechnology products. The Biotechnology Industry Organization (BIO) appreciates the opportunity to comment on the FDA's Draft Guidance for Industry: Pharmacogenomic Data Submissions.

#### **General Comments**

BIO commends FDA for recognizing the significance of the emerging science of pharmacogenomics and the importance of appropriate consideration and use of pharmacogenomic data by the agency. BIO agrees that this science holds tremendous promise that potentially could be slowed or otherwise adversely affected because of concerns about whether and how FDA would use these data for purposes of regulatory decisions. We thus welcome the opportunity to participate in open dialogue with FDA and other stakeholders, through comments on this draft Guidance and by other means, about how and under what circumstances the agency will request pharmacogenomic data and use them.

BIO notes that the draft Guidance does not appear to make distinctions based on the phase of product development during which pharmacogenomic testing is done and data are collected. However, there are in fact major differences in standards, processes, interpretation, use, and impact associated with the generation of pharmacogenomic (PG) data during the various phases of drug discovery and development. Therefore, we suggest that either three separate guidances be developed for non-clinical, clinical, and clinical pharmacology data or, alternatively, that one guidance encompass all three areas but address each separately. BIO believes it is important for any guidance related to pharmacogenomic testing and data to differentiate clearly between data used in the design of a development program (which potentially could be provided to the agency voluntarily) from data used in specific clinical trial design or as a criterion for patient enrollment (that clearly would be submitted under the IND). In addition, BIO believes it is essential that any such guidance describe in detail a process between the FDA and a sponsor through which any data submitted voluntarily could be required by the Interdisciplinary Pharmacogenomic Review Group (IPRG) to be reclassified as data necessary for a regulatory decision. The description of any such process should clearly delineate and explain both the responsibilities of the sponsor and the sponsor's recourse.

#### Data Quality:

It is clear from the background discussion in the draft Guidance that FDA recognizes the importance of data quality and the sensitivity of these kinds of data, particularly in regards to patient privacy. Thus, BIO recommends that any final guidance explicitly state that pharmacogenomic research involving human subjects is covered by GCP/ICH principles, but is outside the purview of other regulatory structures. We also believe it is essential to differentiate pharmacogenomic markers, even known valid biomarkers, from a clinically useful test that must be conducted in a CLIA-certified laboratory. With respect to analytical validation standards, it should be made clear that a pharmacogenomic clinical trial assay will not be held to the standards of an in vitro diagnostic test, even if that assay is used to justify label language (although if the label requires testing prior to prescription, then an IVD may be highly desirable or even required).

Specifically, we recommend that the guidance explicitly state that tissue samples from non-clinical GLP studies may be collected and analyzed with pharmacogenomic methods in an exploratory fashion (not necessarily in accord with GLP requirements), so long as this is clearly indicated in the protocol at the start of the studies. With the lack of standardization and the rapid evolution of pharmacogenomic technologies, it would be difficult, if not impossible, in most situations, to generate PG data that meet current general GLP requirements.

Finally, regarding the archiving of PG data, it is important to clarify whether data will be required to be stored in compliance with 21 CFR Part 11, as these requirements will have implications on processes for data filing.

## Decision Making:

BIO is concerned about the interchangeable use in the draft Guidance of the terms “decision-making” and “regulatory decision-making.” Either terminology should be used consistently or the terms should be clarified in the guidance. Regulatory decision-making (i.e., use of PG data by FDA to make regulatory decisions such as determining approvability or appropriate use or labeling of a product) is quite different from clinical/drug development decision-making by sponsors. We suggest that FDA differentiate reporting requirements between pharmacogenomic data and results of pharmacogenomic testing that drive decisions in a clinical or animal trial to support safety or efficacy and data or testing used for purposes of making such decisions, in a clinical development program, as selection of promising compounds during candidate screen. For example, we believe that genotype results used to screen or select subjects in a clinical trial, or to stratify the primary analysis, should be reported.

## Biomarkers:

BIO is concerned about the definitions, in the draft Guidance, of biomarkers as “known valid,” “probable valid,” and “non-valid.” We strongly urge FDA, in developing any final guidance, to provide clarification and/or further explanation in the following broad categories:

### *Technical*

- The impact of the analytical robustness of assay and other technical specifications of measurement on the status of a marker regardless of its predictive value
- The role for CDRH in the biomarker status process, especially the Office of in vitro Diagnostics
- Allowance for change in marker status when used individually versus collectively, for example, single gene versus gene array
- Allowance for change in marker status when used genetically versus genomically, for example, genotype versus expression level

### *Procedural*

- Mechanism of conversion from probable valid to known valid, from non-valid to probable valid
- Responsibilities to sponsors when biomarkers status changes
- Impact of diagnostic versus prognostic use of a marker on its status

### *Definitions*

- Boundaries between biomarker categories
- Differences even within a given marker category based on relative scientific (research-established) versus medical (clinical utility) merits of marker

### *Suggestions*

- Nomenclature should be revised to delete the term “valid”, and be simplified to “known” versus “probable” or alternatively “emergent” biomarker,

- More weight should be given to use of the markers (rather than their scientific background) in a drug application
- FDA should provide regular reports to communicate changes in biomarker status
- FDA should provide an inventory of biomarkers in valid and probable valid categories, including alleles in the cases of genetic markers; website posting is suggested for ease of communication and updating.
- Industry should be invited to provide its own markers in each category to cement consensus and highlight discrepancies among companies
- A standing committee composed of FDA, industry, and academic representatives should be established to evaluate biomarker status

### Interdisciplinary Pharmacogenomic Review Group (IPRG):

While BIO recognizes the novel nature of genomic data and the need for technical expertise in its interpretation, we are concerned about the proposed “Interdisciplinary Pharmacogenomics Review Group” (IPRG) as described in the draft Guidance. In general, our concerns and questions can be summarized as follows:

#### *Procedural*

- How will members be selected for the IPRG and who will they be? Will there be any crossover; that is, will reviewers be members of the IPRG, or vice versa?
- By what process, and under what circumstances, will the IPRG communicate with each component of FDA, including review divisions? When and how will review divisions request counsel and input from IPRG?
- How will the agency ensure consistency? That is, how will they approach use of the IPRG among review divisions? How will they be harmonized to avoid conflicting review policy?

#### *Relationship to sponsors*

- How will the timing of VGDS be established to allow appropriate review by the IPRG? By what mechanism and through what channels will sponsors be able to communicate with the IPRG and to deal with the group’s genomic data oversight, in addition to working through the review division?
- What will be the role of the IPRG in disagreements between sponsors and review divisions regarding pharmacogenomic data? Will the IPRG be involved in dispute resolution; how? What recourse will sponsors have concerning disagreements with the IPRG itself?
- How will the IPRG communicate cumulative evidence gathered from multiple company submissions to which only the IPRG is privy? How will transparency of important technical information be assured, without jeopardizing confidential commercial information?
- Will there be a mechanism for sponsors to meet with the IPRG to discuss data under VGDS? What would be the timing for any such interaction? What would the IPRG be expected to “deliver” post such communication?

In addition to urging the agency to respond to and provide clarification regarding these concerns, BIO offers to specific suggestions about the IPRG. First, BIO believes that no

IPRG member should be directly involved in regulatory decision-making. Second, we urge that FDA consider the use of an advisory committee to discuss general observations without breaching confidentiality of the data, to assure impartial, state-of-the-art expertise and guidance that also is open to the public.

Format, Content and Timing of Submissions:

In any final guidance, the agency should be clear and specific regarding the nature and content of each type of pharmacogenomic (PG) report to be submitted: complete report, abbreviated report, and synopsis. The structure of these reports should be clearly defined and agreed upon with industry to promote global harmonization of PG approaches. In addition, the guidance should be clear about the content, format and amount of raw data necessary for a required versus a voluntary (VGDS) submission. As the draft guidance points out, and we agree, a consensus does not exist for presenting and exchanging genomic data. However, the suggested content and format ranges widely from no raw data (as would be the case, for example, with an article submitted to a peer-reviewed scientific journal) to submission of electronic files containing all raw data, images, scatter plots, etc. for all experiments, plus validation data. If reporting clinical genomic data through a journal article format is feasible, this would be an acceptable way for reporting aggregate results within the limits of many informed consent protocols.

Further, it is essential for sponsors to know, at least in general, which datasets the agency will be expecting in the submission. There are several ways to address this. Initially, any guidance document should be clear about the agency's expectations. Then, as standards evolve and FDA gains more experience with VGDS, new and additional requirements or expectations may be conveyed to the industry through public meetings or dialogue sessions.

Alternatively or additionally, the agency could provide a mechanism by which sponsors anticipating making a VGDS may meet with appropriate agency representatives to discuss the planned VGDS (One option would be to have this take place as part of a Type 'C' meeting). This would allow sponsors to prepare for when VGDS submissions would likely be made. Interaction between the agency and the sponsor before, during, and after review of the submission by the IPRG is critical - there is a need for feedback to the sponsor regarding the agency's understanding of the data. A formal meeting should be held at the request of the sponsor, at which the sponsor could present their interpretation of the data and the agency can discuss its data needs, including whether it is likely that the IPRG may request additional data. The amount and nature of the information exchange at any such meeting will, of course, depend on the timing of the meeting.

For VGDS in the pre-IND stage, guidance should be provided on whether an IND number should be requested. There is a potential for data much more voluminous than typically occurs with the request for pre-IND meetings.

The desired timing for any VGDS should be outlined to enable the IPRG to evaluate the data most effectively with the appropriate data set. In addition, some guidance as to the

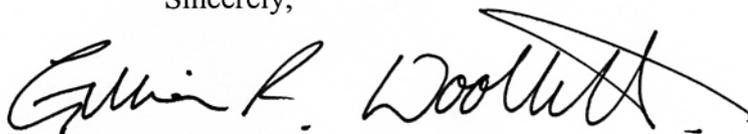
preferred format of the reports along with the potential of integration into primary clinical study or non-clinical study reports would be helpful.

Intellectual Property:

BIO believes that it is necessary that the FDA include commentary on Intellectual Property (IP) connected with VGDS. It is well known that an industry like biotechnology is dependant on its IP and without a well-defined IP stance by the FDA in regards to pharmacogenomic data, companies may be unwilling to submit their data for voluntary review to the agency. Specifically the agency needs to outline a protocol for the assignment of IP rights (both inventorship and ownership) that may potentially be gleaned by FDA staff in the course of reviewing VGDS from several companies. If FDA staff were to discover novel applications of pharmacogenomic markers in safety or efficacy who would own such a discovery and who would have the right to commercialize it? Would the participating FDA scientists have claims as an inventor? BIO recommends that the FDA include a statement that they would not seek to patent any inventions that stem from the use or review of the submitted data. Additionally, there are concerns as to whether VGDS data would be subject to the Freedom of Information Act. Despite reassurances from the FDA (FDA/DIA meeting, Washington, November 2003) that VGDS data is confidential and protected, many companies remain anxious about GDS IP without an agency position on this topic in the guidance document.

Thank you for your consideration of these comments. Please do not hesitate to contact me should you have any questions.

Sincerely,

A handwritten signature in black ink, appearing to read "Gillian R. Woollett". The signature is fluid and cursive, with a long horizontal stroke at the end.

Gillian R. Woollett, MA, DPhil  
Vice President  
Science and Regulatory Affairs