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April 19, 2011

Division of Dockets Management (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2011-D-0082: Draft Guidance for Industry on Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies

Submitted via email to http://www.regulations.gov

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) appreciates the opportunity to submit comments regarding the *Draft Guidance for Industry on Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies.* BIO recognizes the importance of appropriate consideration and use of clinical pharmacogenomic data by the Agency to ensure that this information is used appropriately to improve healthcare outcomes.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnologies, thereby expanding the boundaries of science to benefit society by providing better healthcare, enhanced agriculture, and a cleaner and safer environment. Specifically related to pharmacogenomics, BIO represents companies that develop and manufacture laboratory developed tests, test systems, and targeted therapeutics that may rely upon pharmacogenomic information for optimum safety and efficacy. For this reason, BIO companies welcome the opportunity to work with the FDA as the Agency develops guidance on clinical pharmacogenomic studies through all phases of product research and development. In response to FDA's request for comments regarding the Draft Guidance

for Industry on Clinical Pharmacogenomics; Premarketing Evaluation in Early Phase Clinical Studies, BIO respectfully submits the following comments:

In general, there are 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. BIO appreciates that this Draft Guidance primarily addresses questions pertaining to early phase clinical studies, such as investigation into how early phase data on genomic-dependent dosing can be used to guide later studies or the collection of genetic and biomarker data. It is important to recognize that a small sample size is common for many early phase clinical trials, and all of the recommendations put forth within this Draft Guidance involving sample collection and evaluation of data should take into account the limitations involved with small sample size. We encourage FDA to continue to develop recommendations to address all phases of research and development studies as pertaining to PG. Specifically, recommendations to address statistical considerations used in later phases of randomized clinical trials that are intended to draw definitive conclusions from genomic subgroup effects would be useful to provide clarity and consistency for industry in PG clinical study design.

I. Prospective DNA Sample Collection:

- Language throughout the Draft Guidance focuses on prospective collection of DNA samples from all subjects in clinical studies. However, the strict requirement of conducting prospective clinical trials, including prospective sample collection, for all PG tests and PG information-directed therapeutics is currently an unachievable ideal. The Guidance should recognize that in many instances prospective clinical studies will not be achievable for important PG studies related to existing products.

- While the Draft Guidance does address exclusion of patients with a "clear absence of a drug target" in one instance (line 566), we believe that this aspect of early clinical study design should be expanded upon throughout the Draft Guidance. The qualification of a patient for therapy based on the categorical presence or absence of a genetic marker will be important in exclusion of some patients for enrollment in trials, whereas it may be suitable to enroll patients in cases where the biomarker indicates a varying spectrum of likely influences on response.

- The recommendation regarding the collection of DNA samples from all subjects in all clinical trials can be made more feasible by changing "all clinical trials" (line 318) to "most clinical trials". Formulation bioavailability/bioequivalence (BA/BE) studies is an example of the sort of study for which DNA collection may not be necessary. Another example in which sample collection may not be necessary involves the requirement to conduct Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies in healthy volunteers representing various common genotypes (>1). The amount of prescreening required and the number of subjects to be enrolled to meet this requirement may be unrealistic for early phase studies. A more realistic approach would involve ensuring that metabolizer extremes for well-characterized polymorphic enzymes (e.g., poor metabolizers vs. extensive metabolizers) be enrolled

in the trial where there is a strong hypothesis that genetic variability may be important to the pharmacokinetics.Furthermore, samples should "generally" be collected in all arms of clinical trials, however there are some cases for which sample collection would not be necessary; for example, during a trial in which all subjects are treated with standard-of-care to select for treatment resistance prior to randomization, it should not be necessary to collect DNA samples from subjects who do not progress beyond the standard-of-care portion. We believe these revisions still allow the Guidance to encourage the advancement of pharmocogenomics in product development without being overly restrictive.

- When referring to consent for DNA collection from clinical trial participants (lines 328-330, 353-356), the recommendation should indicate consent "when possible under applicable laws, regulations and IRB/IEC policies". Again, some important cases will not allow for prospective collection of DNA samples. Furthermore, regarding retaining DNA samples (lines 334-335), the Guidance should note that samples should be retained "when possible under applicable laws, regulations, and IRB/IEC policies". Sponsors must obtain consent for storing samples. In cases of mandatory collection, some laws, regulations and policies may require that samples be destroyed subsequent to the test for which they were collected. For example, policy standards in Denmark and the Netherlands require that samples be stored for limited periods to be specified at the time of collection, or only for the time needed to complete the purpose pursued in banking the samples. Other examples of DNA sample collection and coding obstacles, and harmonization efforts have been described recently in the following referenced articles:
    - D S Ricci, E D Broderick, A Tchelet, F Hong, S Mayevsky, D M Mohr, M E Schaffer, A W Warner, P Hakkulinen, A Snapir. Global Requirements for DNA Sample Collections: Results of a Survey of 204 Ethics Committees in 40 Countries. *Clinical Pharmacology & Therapeutics* 89, 554-561 (2011)
    - M A Franc, N Cohen, A W Warner, P M Shaw, P Groenen, A Snapir . Coding of DNA Samples and Data in the Pharmaceutical Industry: Current Practices and Future Directions—Perspective of the I-PWG. *Clinical Pharmacology & Therapeutics* 89, 537-545 (2011)

- The National Institutes of Health (NIH) has published recommendations for consent for broad use of genomic data and samples, including the use of de-identified samples. The FDA should consult with NIH on this topic. This is particularly important for samples collected in early phase clinical trials that could potentially be retained for a number of years.

- Consistent with previous pharmacogenomic guidances, the scope of the current Draft Guidance encompasses both DNA and RNA (as stated in the Background, line 47). However, the Draft Guidance has a strong emphasis on DNA, with all examples provided being DNA-based. If the Guidance is to encompass both DNA and RNA, we recommend including examples of RNA markers, to address any special considerations that would be relevant to RNA samples/data/tests, and to refer to both DNA and RNA throughout.

- BIO urges FDA to promote educational efforts necessary so that patients and Institutional Review Boards (IRB) / Independent Ethics Committees (IEC) understand that patient privacy will be maintained for participants in clinical studies and that the informational and privacy risks associated with DNA collection are indistinguishable from those associated with the collection of other medical information in clinical trials. We believe such educational efforts will be critical to the development of an atmosphere that will allow for more widespread DNA sample collection.

II. Clinical Evaluation of Pharmacogenomics:

- The Draft Guidance gives the overall impression that sponsors should have a reasonably good understanding of predictive markers prior to entering phase III pivotal studies. While ideal, this is not supported by the realities of genomic analysis or clinical development. We believe that it is unrealistic to have "full ascertainment of genomic status of every randomized subject" in early development (lines 231-232)". In most cases, hypotheses may be lacking pre-approval and clinical effects may be too small to detect with available sample sizes. Furthermore, PG data are frequently gathered retrospectively, and the Guidance should clearly acknowledge that evaluation of prospective clinical data may not always be possible.

- Clinical studies dedicated to PG information are uncommon. PG data are more frequently collected as an exploratory activity in the context of ongoing broader clinical trials. The Guidance should clearly acknowledge that PG data collection should be adapted to the primary goals of clinical trials, rather than presuming that PG data is the primary goal of a given trial.

- The Draft Guidance recommends that analytical validation of genotyping and phenotyping methods should be established before initiating a clinical PG study. While this is generally understood for assays to develop definitive results in later stage clinical trials, it is not immediately clear for early phase exploratory studies. The Guidance needs to clarify the level to which these assays must be validated.

- The Draft Guidance proposes clinical PG investigations for drugs that are found, *in vitro,* to be metabolized "*to a large degree*" by a polymorphic pathway (lines 433-434). We propose to clarify what is considered "*to a large degree*". Similarly, the Draft Guidance refers to "…*if important variability in PK of active species is observed*…" (lines 482-483). It is not clear what the Agency considers "important" variability. We recommend that the Guidance provide some general guidance on what is considered "*important*" variability. For example: % CV (coefficient of variation) of a PK (pharmacokinetic) parameter larger than a certain cutoff value.

- Currently there is a lack of standards for sequencing platforms. In the future, most genomic samples could be sequences, and the FDA should partner with the National Institute of Standards and Technology (NIST), technology developers, international standards bodies (e.g. Clinical and Laboratory Standards Institute (CLSI)) and professional societies to develop standards for sequencing technologies.

III. Principles of Including Pharmacogenomic Information in Labeling:

- BIO appreciates the need to make recommendations for clinical evaluation pertaining to product labeling, but note that the premarketing evaluation/early phase of clinical studies may not always yield the complete results that are applicable to labeling decisions more commonly associated with later phase clinical studies.

- The FDA should provide guidance that encourages drug manufacturers to describe diagnostics based on their molecular entities for applicable drug labels. Referencing a diagnostic test based on a brand name could imply FDA endorsement of that test over other commercially available tests and should be carefully considered and only permitted under unique and appropriate circumstances.

- PG information in labeling should also potentially include negative results of clinical studies involving strong candidate genes. This information is often not published, but its inclusion could be useful to help avoid future futile PG research.

Conclusion:

BIO greatly appreciates the opportunity to provide these comments to FDA regarding clinical pharmacogenomics. We are united in our goal to provide patients and healthcare providers with safe, accurate, and effective therapies and diagnostics so as to best serve the needs of the healthcare system. We are also united in our recognition of the potential of clinical PG information to improve healthcare outcomes. We believe that these comments will help to encourage the advancement of pharmacogenomics without compromising the regulatory environment, and we look forward to further opportunities to provide feedback.

Respectfully submitted,

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