



Comments Provided to the  
US Food and Drug Administration  
by the  
International Society for Pharmacoepidemiology  
(ISPE)

Considering:

Guidance for the Industry  
Pharmacogenomics Data Submission

February 3, 2004

## **BACKGROUND**

The US Food and Drug Administration published the draft guidance on the submission of Pharmacogenomics data in support of investigation new drug application (IND), new drug applications (NDA) and biologics license applications (BLA) applications. The guidance is prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. Comments are solicited on the draft guidance (FDA Docket No. 2003D-0497). This report is in response to this request.

## **COMMENTS ON DRAFT GUIDANCE**

The International Society for Pharmacoepidemiology (ISPE) fully supports Agency efforts to clarify and publish guidelines related to pharmacogenomic (PG) data submission. The Society's interests in providing comments derive from its mission statement, which clearly states the Society's interest in policy development as pertaining to the areas of pharmacoepidemiology and therapeutic risk management. Pharmacogenomics is emerging as an important modifier of the benefit to risk ratio for drugs and biologicals. In review of the guidelines, the Society would like to offer the following comments and suggestions. These comments do not necessarily reflect the view of all its members or provide all comments that its members may have on the guidance to pharmacogenomic data submission.

The guidance provides a well-documented overview of the Agency's current thinking concerning the inclusion of Pharmacogenomic data submission as part of an IND, NDA or BLA.

The background and the introduction section are well outlined. However, the document does not discuss pharmacogenomic data in the context of therapeutic risk management. (lines 43-45). The passage of the PDUFA III agreement highlights the importance of risk management plans as an important part of the approval process. The guidance states: "The promise of pharmacogenomics lies in its potential ability to identify sources of interindividual variability in drug response (both efficacy and toxicity)." Placing pharmacogenomic data in the therapeutic risk management context would also allow for a clearer inclusion of this information in patient package inserts. Although approximately 160 drug labels include various levels of pharmacogenomic information, it is not clear how the clinician should use this information, or what the relevance of the information is for the efficacy and the safety of the referred drug products.

Several classification systems are offered in the draft guidelines. However the operationalization of these classification systems is not clear, and is, in their current stage of development and definition, open to multiple interpretations. The FDA emphasizes that data submission is determined on the basis of the nature of the PG markers. FDA classifies the markers into a) valid; b) probable valid and c) explorative markers (lines 128-145; 591-612). While this classification provides a useful framework for regulatory decision-making, the basis for the classification may not always be apparent.

The guidance states that the difference between a “valid” and a “probable valid biomarker” is that the latter “may be not yet widely accepted or have been independently replicated (line 137-139).” This could be open to interpretation. For example, if a sponsor has demonstrated the clinical significance of a well-understood marker (e.g. tumor-antigen) in two separate clinical studies, but the marker has not been widely studied in the scientific community (for reasons as diverse as time constraints or lack for resources, or viable funding). Would this prevent the marker from being considered as a “valid” marker? Further clarification and interpretation is needed on this point.

Also, the Food and Drug Administration refers in the guidance document that it is developing several other guidance instruments in the field of pharmacogenomics. Specifically, it refers to “guidance on co-development of pharmacogenomic tests and drugs (lines 206-208), and “specific guidance on how to submit detailed reports of pharmacogenomic research to INDs, NDAs and BLAs” (line 469-470). We believe that the interpretation of this current guidance document is likely to be subject to specifics in those upcoming documents /efforts. Therefore, it may be helpful to publish these documents simultaneously (as opposed to consecutively) to fully appreciate the significance and to interpret these documents appropriately. Would it be possible NOT to finalize this current document until the community has had an opportunity to review these additional guidance papers?

The purpose of the Voluntary Genomic Data Submission (VGDS) is described as “to provide the FDA access to emerging pharmacogenomic data so that a foundation can be built for developing scientifically sound regulatory policies.” It also states that this data will be shared. (line 419-426). Although laudable, it may conflict with a business model where some of this information is considered proprietary. Data sharing agreements and approaches need to be further detailed.

The FDA recommends voluntary data submission on pharmacogenomic data that are exploratory in nature and that are insufficient for regulatory decision-making. It is not entirely clear whether this may have any impact on potential review time (e.g., to support the initiation of first in-human study), and division of review responsibilities within the Agency. In this regard, we welcome further information on the to-be established cross-center “Interdisciplinary Pharmacogenomic Review Group (IPRG)” (line 240-243).

From the perspective of (molecular) epidemiology, we welcome further clarification regarding epidemiology/population data in developing pharmacogenomic markers. For example, what evidence is required to consider a marker as “valid” with reference to its population distribution or predictive value in a given disease? This has not been implicitly discussed in this or other guidance documents (e.g., in vitro diagnostics). We do not recommend that such data are routinely required given the complexity of such testing, but we welcome FDA’s guidance in this regard.

There has been a growing number of pharmacoepidemiologic studies conducted to investigate safety concerns of drugs raised from postmarketing adverse event reports. The identification of risk factors or high-risk subpopulations has often been an important part

of the objectives for this type of studies. Genotype or gene expression profiles could be studied as potential risk factors along with other variables such as age, gender, race, comorbidity, and co-medications. Therefore, it would be useful to provide some guidance regarding how the PG data collected in pharmacoepidemiologic studies would be submitted or used by the FDA.

In a last comment, the guidance seems to reflect the unwritten notion that pharmacogenomics is a deterministic science. However, in its current state pharmacogenomics has not advanced to where a definite prediction is given for an expected outcome. Many outcomes will always have multiple separate determinants. Rather, pharmacogenomics may in some cases predict with a greater certainty, a higher probability of what the response of the individual will be to a drug or biological.

ISPE appreciates the opportunity to offer its constructive comments to the FDA on this important topic. We look forward to continued collaboration.