

NIH Comments on FDA's Draft Guidance for  
Industry Pharmacogenomic Data Submission  
Docket No. 2003D-0497

We are writing in response to the request for comments on the Food and Drug Administration (FDA) draft *Guidance for Industry Pharmacogenomic Data Submission* published in the November 4, 2003 *Federal Register*. The National Institutes of Health (NIH) strongly supports FDA's effort to address proactively the use of pharmacogenetic and pharmacogenomic (collectively referred to as PGx) strategies in drug development and utilization. The science and technology underlying PGx applications are evolving rapidly, and the draft guidance is a positive step aimed at promoting the application of PGx knowledge to improve public health while acknowledging that further research is still needed. In particular, we commend FDA for taking a creative approach to guidance in an important scientific arena, for the use of a "safe harbor" mechanism to encourage data submission, and for differentiating between research and regulatory uses of the data. While supportive of the draft Guidance in general, NIH has several specific suggestions for FDA's consideration.

**Recommendations**

It would be helpful if the Guidance could provide more specific guidance in several areas. First, the Guidance should be clearer about how the agency will decide when PGx data will be required for submissions of Investigational New Drug applications, Biologics License applications, and New Drug applications. Moreover, it would be helpful to clarify the criteria that will be used to determine what constitutes a "valid biomarker" and a "probable valid biomarker." As written, the draft Guidance simply states that the same rules that are applied to other biomarkers (e.g., serum) will be applied to PGx biomarkers. Since current data on the clinical significance of any given single nucleotide polymorphism (SNP) and the clinical validity of expression associations are lacking, this standard will be very difficult to meet. Further, given how many SNPs and expression patterns exist, carrying out the epidemiological research needed to determine their clinical significance will be daunting. To the extent possible, the Guidance should identify minimum acceptable standards of validation for PGx data and be updated frequently when new data warrants it. Without such minimums, sponsors and investigators are likely to avoid using PGx data or developing PGx tests for fear of undermining products in "susceptible" product development phases, where questions as to validity of the data can cause development delay or investor concern. Moreover, this could have public health implications if it delayed development and marketing of important PGx tests.

Second, the Guidance could be clearer and more specific regarding the definition of Voluntary Genomic Data Submissions (VGDS), the kind of data that should be submitted on a voluntary basis, how the voluntarily submitted data will be handled, stored, and distributed, and how and by whom such data will be evaluated. Will VGDS be reviewed in the context of other data submitted for regulatory purposes? Will they be associated with the submitter? In addition, the Guidance should be clearer about whether VGDS will ever be used for regulatory decisions. In particular, the Guidance states at line 311 and 498 that data submitted voluntarily will not be used for regulatory purposes. However, this assurance appears inconsistent with the statement at lines 312 -314 that "if additional information becomes available that renders the results required to be submitted . . . the sponsor must submit the data to the IND, BLA, or NDA." It would be helpful to clarify what "renders the results required to be submitted" means and how this determination will be made. Will these decisions be made on a case-by-case basis? Will they be made

unilaterally or through a consultation process with the sponsor? We would recommend that FDA develop a data template to guide data submission. Such a template would help submitters but might also be useful to the FDA as an efficient means for data aggregation and analysis. We would recommend that clear mechanisms for resolving disputes that might arise about the validity of a biomarker be in place and spelled out in the Guidance. In addition, we believe that if incentives beyond the safe harbor mechanism for voluntary data submission were provided, the Guidance might be more effective in achieving its intended purposes.

While NIH believes the Guidance will be beneficial overall, we are concerned that it might also have unintended negative effects on the willingness of sponsors to share PGx data. The FDA should clarify whether VGDS data will be considered confidential commercial information and, as such, not publicly accessible. If the data are considered confidential, we would urge FDA to work out a way to blind or aggregate the data so that it can be made available without compromising its proprietary status.

Pharmacogenomic data is developmentally sensitive. For example, since drug response expression patterns change throughout life, findings from one age group will not necessarily apply to another. As such, the Guidance should promote the submission of data from all age groups.

It would be helpful if the Guidance could also explain how pharmacogenomics may affect designation of orphan exclusivity for drugs. For example, if validated pharmacogenomic tests lead to the conclusion that certain small subsets of a population demonstrate selective response to a drug product, will each intended use be accorded orphan drug status?

We also believe that the goals of the Guidance could apply to proteomic data as well as PGx data. The field of proteomics is developing quickly, overlaps with pharmacogenomics in significant ways, and is equally in need of guidance about how it could and should be used in the regulatory process. We, therefore, urge FDA to incorporate provisions into the Guidance that could accommodate proteomic data submission or, if more appropriate, develop a separate Guidance for proteomics.

## **Conclusion**

The NIH appreciates the opportunity to comment on the draft *Guidance for Industry Pharmacogenomic Data Submission* Guidance and commends FDA for developing an approach that is sufficiently in touch with cutting-edge science, yet flexible enough to accommodate further and perhaps unpredictable developments in the field.

We would welcome the opportunity to assist FDA in the further refinement of the Guidance, particularly determining what voluntary data would most be useful and the standards for determining the validity of PGx. The trans-NIH Biomedical Information Science and Technology Initiative (BISTI) Consortium and the Pharmacogenetics Research Network are two programs of particular relevance that could, respectively, provide a forum for further collaboration and serve as a model for data collection. Less structured opportunities for discussion and development of policies and practices concerning PGx data would be welcome, e.g., interaction with NIH scientific experts in the relevant research fields.