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## Global Research & Development

February 3, 2004

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

**Re: Draft Guidance for Industry: Pharmacogenomic Data Submissions**  
[Docket No. 2003D-0497, 68 *Federal Register*, 62461-62463, November 4, 2003]

Dear Sir or Madam,

Thank you for the opportunity to review the Draft Guidance for Industry: Pharmacogenomic Data Submissions [Docket No. 2003D-0497, 68 *Federal Register*, 62461-62463, November, 4, 2003].

Our comments are attached.

We would also invite direct dialogue with the Agency if you would consider the opportunity valuable.

Sincerely,

A handwritten signature in cursive script that reads "Melissa S Tassinari".

Melissa S Tassinari PhD, DABT  
Senior Director  
World Wide Regulatory Policy and Intelligence  
Pfizer Global Research and Development

2003D-0497

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## **General Comments**

Pfizer welcomes the opportunity to comment on the Food and Drug Administration's (FDA) Draft Guidance for Industry: Pharmacogenomics Data Submissions that represents the latest regulatory thinking on pharmacogenomics. This document raises awareness of key issues in the development and application of an emerging science and provides a very important context for dialogue between industry and FDA. We believe that the emerging science of pharmacogenomics requires co-operative approaches from industry, FDA and the academic scientific community if it is to realize its promise.

We welcome the establishment of criteria, based upon suitability of data for regulatory decision-making, that explain which data are required to be submitted. However, in the guidance document a significant emphasis is placed on definitions of biomarker validation, which require further clarification. While the notion of validation may have specific meaning in the regulatory environment, we believe that the development of consensus guidelines involving industry, FDA and the scientific community is required to produce the most satisfactory and generally agreed definitions. Broad expert groups drawing upon these kinds of expertise such as the ILSI Health and Environmental Institute's Subcommittee on the Development and Application of Biomarkers of Toxicity are examples of how such groups are beginning to address some of the issues this draft guidance touches upon.

The proposal to establish voluntary submissions of pharmacogenomic data to the FDA (VGDS) is more problematic. The primary stated purpose for VGDS is to 'provide FDA with access to emerging pharmacogenomic data so that a foundation can be built for developing scientifically sound regulatory policies' [lines 419-20]. We believe that there are many opportunities for FDA to work with cross-industry consortia on the generation of, and access to, relevant data. In addition, there are publicly available data sources (such as the Pharmacogenetics and Pharmacogenomics Knowledge Base) that FDA could work with to gain scientific understanding in this area. We also believe that the peer-review process provides the most valuable route to emerging science in the field of pharmacogenomics. While we support the purpose of VGDS, we believe that the proposal is not workable in its current format. We therefore suggest that the VGDS process be removed from the proposed guidance at this time.

Our comments have been grouped under the following headings and specific lines of text are noted as appropriate

## **Scope and Application of Guidance**

Dr. Woodcock's discussion of the draft guidance at the DIA meeting November 13-14<sup>th</sup>, 2003 indicated that the scope of the present guidance does not include the use of genomics in drug discovery. However, the guidance does not state that discovery applications are out of scope. This guidance should be clear on the scope of the data to be considered.

Additionally, the Agency should clearly state in this guidance that sponsors will be allowed to sample material from GLP studies for research purposes using pharmacogenomic approaches and that submission of these data will not be required.

## **Definitions of terms**

The guidance is titled *Pharmacogenomics* Data Submission but also refers to Voluntary *Genomic* Data Submission. We suggest that one term (genomics or pharmacogenomics) be used to improve clarity.

Given the reference to biomarkers consistently throughout the document, the Guidance needs to be explicit when referring to biomarkers defined by RNA or DNA as 'genomic biomarkers.'

We suggest that term 'data' is substituted for 'test' in the document as the latter conveys diagnostic connotations.

## **Submission Policy**

In the present guidance, it is unclear whether the decision to submit data (according to the criteria outlined in Appendices A & B) will remain with the Sponsor. Clarification of this point would be welcomed.

The guidance suggests [Lines 206-19] that, if a new pharmacogenomics test is to be used in therapeutic decision-making, the Sponsor should also seek approval from CDRH. This is appropriate if the test has a potential clinical or commercial use. However, if the pharmacogenomics test is being developed simply to improve our understanding of the effect of genotype on drug response, the study may conclude there is little or no effect. In this case, work with the CDRH would not be appropriate. It is suggested that this recommendation be removed until the Agency has developed guidance on co-development of drugs and devices.

## **Characterization and Validation of Biomarkers**

The draft guidance offers categories of biomarkers (valid, probable, etc.) and definitions are provided. However, we believe that further scientific debate and the establishment of agreed standard criteria on definitions and application of biomarkers are required. For example, it is not clear how the criteria 'widely accepted in the scientific community' are to be achieved. Similarly, what criteria are required to achieve the status of 'known valid'? It is important to note that validation is often specific to the use of a test for a particular purpose. For example, we would not consider the genotyping of CYP2D6 to be a valid biomarker for identifying intermediate metabolizers, though it may be valid for the identification of poor metabolizers

The value of a definition of a probable biomarker is not clear. The provision of a list of Known Valid Biomarkers would help to address some of the concerns here and would be valuable to sponsors. We suggest that a regularly updated 'living' list be created and published on the FDA web site.

Independent analysis of pharmacogenomic data may lead the Agency to draw different conclusions from a Sponsor. The course of action that will be taken in such an event needs to be transparent. For example, will the Agency define gene expression signatures that the Sponsor must validate as biomarkers? If so, the validation required to consider gene expression signatures as biomarkers also needs to be clarified

The guidance should provide clear directions for the situation where biomarkers generated using relatively new pharmacogenomics technologies would need further validation with more established methods. An example would be gene expression changes identified on a microarray that are then independently validated using a more established technique such as RT-PCR.

## **Voluntary Genomic Data Submission (VGDS)**

The FDA states that many of the pharmacogenomic testing programs developed by sponsors are for the purpose of establishing the validity of novel biomarkers and until that validity is confirmed, the data cannot be used in making regulatory judgments. However, the FDA encourages the submission of such data by the Sponsor, to "advance the understanding of relationships between genotype or gene expression and responses to drugs..." (lines 152-153). As stated above, it is our suggestion that this section of the guidance be removed at this time.

We suggest that it is more appropriate for progress in the advancements of understanding to be through the use of reports generated in the scientific literature, than it is to provide what may be very preliminary data'. This becomes particularly problematic when considering the criteria outlined by FDA for the validation of biomarkers. The guidance indicates that a biomarker may develop over time in terms of its validity (i.e. from

exploratory to probable valid to known valid) as more data becomes available and through voluntary submissions to the Agency. However, given the current definition of 'known valid biomarker' the VGDS alone would not be sufficient to change a biomarker's status as it clearly states a known valid biomarker must be "accepted in the broad scientific community" (lines 136-137). This is not possible through VGDS as the data remain proprietary and confidential. We remain concerned as to how and when voluntary submitted data become suitable for regulatory decision-making and in turn becomes a submission requirement. The pathway and procedures that would be followed are not clearly defined in the current draft guidance. It is particularly important that the constitution and remit of the Interdisciplinary Pharmacogenomics Review Group (IPRG) and the nature of its interaction with the Review Divisions be clarified to ensure that voluntary submissions would not influence regulatory decision-making on INDs or NDAs.

Because any data submitted to the Agency under VGDS are exploratory in nature, these data will almost certainly be proprietary. . A process that ensures intellectual property is appropriately safeguarded should data be submitted voluntarily, outside of an IND, NDA or BLA would need to be determined. If a VGDS process remains in the guidance, clearer statements should be included to describe in the guidance about how sponsors' intellectual property will be safeguarded during the VGDS process. In addition, the creation of an aggregate genomics database of VGDSs [line 419] raises questions on how the agency will make use of the data submitted by more than one sponsor company. According to the guidance, if information becomes available, the Agency will notify sponsors about its determination and that sponsors may need to submit the data to the IND, NDA or BLA (lines 503-507). Such data may come from results made available from more than one Sponsor. In the situation where such data has been presented to a peer-reviewed journal, there is an opportunity for interested parties to review and independently assess the data. However, if the Agency makes a decision on a Sponsor's product, based on proprietary information from another company (provided via VGDS), will the affected Sponsor will have an opportunity to review and independently assess the data that led the Agency to require submission of data to the IND. NDA or BLA?

These are key issues in the development of a new scientific framework for the evaluation of pharmacogenomics data as proposed by FDA and may discourage rather than encourage the voluntary submission of pharmacogenomic data. If so, this could have the unfortunate consequence of impeding rather than encouraging the development of the science.

## **Analysis and Reporting of Data**

Pharmacogenomic data, in general, are multi-dimensional and different approaches to analyzing the data often lead to different interpretations. If data submissions are needed/required then complete data should be submitted instead of subsets of data. This would be necessary to capture correlation structure when computational approaches, such as permutation tests, are used to find proper cut-offs for controlling a study-wide error

rate. If the Agency wishes to analyze the data, then a subset of data will not be sufficient. This raises the question of how sponsors can be sure that appropriate statistical models would be used by Agency personnel. This applies also to array data when the whole dataset is required for the normalization procedures. If the Agency wishes to review normalization procedures for microarray data, complete datasets will be required. As noted above, how will the Agency maintain the intellectual property protections for the Sponsor?

In many circumstances pharmacogenomics data may be generated under additional privacy and data protection procedures such as anonymization or de-identification. What degree of detail of reporting of pharmacogenomic data would be appropriate, so that concerns and regulations (e.g. HIPAA) are taken into account? The guidance should address these issues, to assure sponsors that the FDA would accept such procedures to protect the privacy and confidentiality of patients.

We propose a broader definition of the types of data format the Agency is looking for in terms of abbreviated reporting format and structure. We would note that data tabulations are essentially the same for full or abbreviated reports. We encourage the Agency should agree to work with recognized expert consortia such as International Life Sciences Institute (ILSI) in order to address these areas.

Gene expression profile data can be used to identify targets and biomarkers, characterize *in vitro* tools, and increase understanding of compound and disease mechanisms. Analysis of gene expression signatures generated in discovery exploratory studies can lead to identification of statistically significant changes that may have no relationship to the physiological and/or clinical data associated with the samples. Application of the technology in the clinical settings will lead to similar observations. The Agency needs to clarify how it will use gene expression profile data particularly as many of the associations generated will not be replicated at a later date.

## **Format and Content of Data Submissions**

Section IV on Submission of Pharmacogenomic Data should describe how to submit the data and where to include it within the current guidelines<sup>1, 2</sup>. This issue is applicable in all other areas that discuss the submission of data and reports; such as the VGDS section [starts on line 408] and annual reports [line 384]. In addition, line 384 states that "known or probable valid biomarkers must be submitted in the annual report" for approved NDA or BLA. This implies that the Annual Report guidelines will be expanded to include this

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<sup>1</sup> U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologic Evaluation and Research (CBER), Draft Guidance for Industry for Providing Regulatory Submissions in Electronic Format -- Human Pharmaceutical Product Applications and Related Submissions, August 2003.

<sup>2</sup> U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologic Evaluation and Research (CBER), Guidance for Industry for Providing Regulatory Submissions in Electronic Format -- General Considerations, January 1999.

information; however, no guidelines or specifics are given. FDA needs to provide guidance on how these data will be incorporated appropriately.

Guidelines on the data that might be contained in a report on a gene expression array experiment [lines 437-67] contain some inaccuracies. For example, DNA quality is not an issue for the conduct of a gene expression study while validation of a SNP by SSCP does not occur in RNA studies. In addition, the use of one technology platform to validate data generated from another technology requires careful elucidation.

This section should also reference the eSub general guidelines<sup>2</sup> specifying what file formats are acceptable for raw images, data etc.

## **Conclusion**

We find that this guidance document is a welcome contribution to the debate on the development of the science of pharmacogenomics and illustrates some potential key steps to the development of consistent and scientifically robust regulatory guidelines. In particular we welcome the clarification of requirements for the submission of data to FDA. We have concerns about the proposal for VGDS we which we detailed in our comments and we welcome the opportunity for further debate on the evolution of this guidance.

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<sup>2</sup> U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER) and Center for Biologic Evaluation and Research (CBER), Guidance for Industry for Providing Regulatory Submissions in Electronic Format -- General Considerations, January 1999.