COMMENTS ON DRAFT GUIDANCE FOR INDUSTRY ON PHARMACOGENOMIC DATA SUBMISSIONS [DOCKET NO. 2003D-0497], FEDERAL REGISTER NOTICE: NOVEMBER 4, 2003 (VOL. 68, NO. 213, 62461-62463)

OVERALL COMMENTS

On November 4, 2003, the Food and Drug Administration (FDA) issued the above referenced Federal Register Notice soliciting public input on draft guidance to industry on Pharmacogenomic Data Submissions. The draft guidance provides recommendations to sponsors holding investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) on what pharmacogenomic data to submit to the agency during the drug development process, the format of submissions, and how the data will be used in regulatory decision making. The draft guidance is intended to facilitate scientific progress in the area of pharmacogenomics which should enable the FDA to use pharmacogenomic data in regulatory policies and decision making.

The unravelling of the human genome and advances in genetic research are now opening up new horizons in the understanding of the science behind the variability between individuals. GlaxoSmithKline (GSK) is a leader in the conduct of pharmacogenomic research to provide safer and more effective medicines for patients. We applaud FDA for their willingness to partner and work with Industry to develop this guidance as well as for their acknowledgement of the 'state-of- the-art' regarding pharmacogenomics. FDA's intent to issue further guidance on the co-development of pharmacogenomic tests and drugs in the near future is fully supported. It is considered that such guidances are as imperative for Reviewers and the IPRG as they are for Industry if appropriate and consistent use of pharmacogenomic information through provision of a clearly delineated, predictable, process is to be ensured.

The ongoing dialogue between Industry and FDA and activities such as the recent joint workshop to discuss VGDS are welcomed and supported. It is hoped too that FDA will continue to liaise globally for a harmonized approach that is supported by all major regulatory agencies given the potential global regulatory impact of pharmacogenomics on drug development.

GSK believes that the guidance, with suggested modifications, provides a reasonable framework to facilitate scientific understanding and progress in the field of pharmacogenomics through the free exchange of information. Additionally, the guidance is beneficial in promoting the use of certain pharmacogenomic data in informing regulatory decisions for the improved use of medicines.

The provision of a process whereby companies may share exploratory pharmacogenomic data with FDA whilst having the mutual goal of advancing the state of scientific knowledge without impeding the progress and generation of such data, or the availability of new and needed treatments for patients, is welcomed and fully supported. In addition, GSK considers it critical that there is an ongoing information exchange between FDA and Industry to share the educational benefits and insights gained through the VGDS initiative.

It is also believed, however, that there are significant opportunities to further the utility of the guidance, particularly with regard to critical definitions (and related implications) such as biomarker definitions as well as the details pertaining to when and how data will, and will not, be used for regulatory decision making.

The areas where GSK advocates revisions to the guidance are summarized in this document.

GENERAL COMMENTS

?? We suggest that the guidance should be intended for both Industry and FDA (IPRG and Reviewers). **[cover page]**

?? It is assumed that, once issued, the guidance would be applied only to ongoing investigations and new marketing applications. **[lines 139, 278 and 340]**

?? It is unclear why proteomics is excluded from the guidance. It would be helpful for the science to have clarity on handling these exploratory biomarker data, and indeed other 'omics' such as metabolomics, and thus permit sponsors to submit such data for review and discussion under VGDS. **[line 31]**

DEFINITIONS

?? The definitions for pharmacogenetics and pharmacogenomics appear to have unnecessary and confusing overlap i.e. *"interindividual variation in DNA sequence related to [pharmacokinetics] or [pharmacodynamics]"* defined in pharmacogenetics *and "interindividual variations in whole genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers*….." defined in pharmacogenomics, whereas the latter are actually approaches to conducting the former.

It is suggested that both of the definitions noted above are applied to pharmacogenetics (i.e. related to DNA) and that pharmacogenomics relates specifically to the analysis of gene expression and its products. **[lines 26-33]**

?? The draft guidance makes reference to a "biomarker", "valid biomarker", "known valid biomarker" and a "probable valid biomarker". Which of the three categories the sponsor assigns determines the level of reporting details. Whilst it is

understandable that data used for regulatory decision making should require mandatory submission, the value of implementing a "validity gradient" is questionable and will likely result in confusion and inconsistent application by various sponsors. GSK suggests that the primary point of emphasis for the submission decision algorithm be whether the data are used for regulatory decision making and offers the following suggestion for such a definition:

Pharmacogenomic data used for "regulatory decision making" are data sufficiently established to make assessments regarding the safety and efficacy of the drug (i.e. predictive value) that guide:

- *the sponsor's decisions regarding the design or selection of non-clinical or clinical research studies, or*
- *a regulator's determination of the acceptability of proposed biomedical research, or*
- *a regulator's determination of approvability of a marketing application, or change in the recommended conditions of marketed product use (e.g. labeling)*

Pharmacogenomic data that are used for all other purposes can be considered as not used for Regulatory Decision Making.

GSK would advocate that pharmacogenomic data for biomarkers that are used for regulatory decision making (as defined above) should require mandatory submission to FDA. Studies of all other biomarkers would be encouraged under VGDS for INDs, NDAs, and BLAs.

If FDA determines that the proposal for categories of biomarkers should be retained (described above as a "validity gradient"), we feel that the Agency will need to address the practical considerations of ensuring that all parties share a common understanding and provide clear guidance as to how all may consistently determine the appropriate category for regulatory reporting purposes.

As noted on line 126, the distinction of a biomarker will evolve over time. GSK suggests that if a category, rather than the action taken, is the focus, the only means by which all sponsors can share a common understanding of the regulatory implications of a given biomarker is if FDA were to maintain, and make available publicly, a list of what the Agency considers to be "known valid biomarkers". If this approach is taken, the Agency should replace the term "known valid biomarker" with "approved (or accepted) biomarker" as this would be a more accurate reflection of the relevance to the regulatory process. Such a list should specify the conditions under which the biomarker has been judged "approved". FDA should also include in the category of "approved" those biomarkers that individual sponsors have established with the Agency as

sufficiently clinically significant to be used for regulatory decision making. Submission of all other biomarker data (i.e. that are not used for regulatory decision making) should be encouraged under VGDS.

Even though GSK has proposed the alternative above for an FDA-maintained list, it is recognised that FDA may not wish to pursue this course of action. Therefore, GSK urges the Agency to base its guidance for regulatory reporting on those biomarkers used for Regulatory Decision Making (i.e. the definition proposed previously) rather than a subjective decision about the acceptability of the biomarker to FDA and / or the scientific community at large.

?? Described below are some of the specific issues that will need to be addressed if FDA determines that it wishes to retain the proposed categories for biomarkers:

- There is a need to better define the terms "valid biomarker", "known valid biomarker" and "probable valid biomarker" to aid transparency and predictability for sponsors.

- In addition, the purpose of the "biomarker" (e.g. diagnostic, predictive, prognostic) should also be specified to ensure common understanding with regard to the utility of the information.

- It would be particularly helpful to Industry if representative real examples from FDA were included for what are considered to be known valid and probable valid biomarkers (including for the drug metabolizing cytochrome P450 enzymes), both for the IND phase as well as for the unapproved or approved NDA / BLA phase of the regulatory review of such data. **[lines 121-141]**

- It would be beneficial to Industry if FDA elaborated on what constitutes an *"established scientific framework or body of evidence"* for a valid biomarker with specific examples. Also, It is suggested that the definition of a "probable" biomarker as referenced in the guidance to "*data being generated within a single company* "or *"without independent replication of data*" be further clarified with regard to multi-center / investigator, multi-studies for a given biomarker evaluation and validation assessment. **[lines 130, 138-139 and 607-608]**

- FDA also references a probable valid biomarker as having *"…..a significant association between a pharmacogenomic test result and clinical outcomes…..*". It is noted that whilst a significant association may be evident between test results and drug responsiveness, the association with a clinical outcome may be a significant hurdle to clear. FDA is requested to provide additional clarification and examples and also to consider associations with surrogate endpoints in addition to clinical endpoints. **[line 140]**

- FDA is requested to define in more detail the process for the transition from "exploratory" pharmacogenomic data to "probable" valid biomarker and

ultimately to "known" valid biomarker, together with what FDA sees as the consequences and requirements for the sponsor regarding such transitions. **[lines 128-145]**

USE OF PHARMACOGENOMIC DATA IN REGULATORY DECISION MAKING

?? FDA is requested to clarify what is meant by "use in decision making" at both the IND and the NDA / BLA stages, and to provide additional examples of when the data will, and will not, be used in such a manner. GSK would advocate for defining and distinguishing between "Decision Making" and "Regulatory Decision Making". **[lines 62-63, 107-109 and 115-119]**

For example, "observational" (non regulatory decision making) pharmacogenomic data from a given study with a pharmacological agent that are not used to affect or support subsequent study designs / patient selection / stratification / regulatory decisions for that drug, or that are used to make decisions regarding the drug development program of another pharmacological agent, would be eligible for submission under VGDS. However, such data being used "directionally" (regulatory decision making) for a subsequent clinical trial design such as subject selection / screening, or used to support regulatory decision making for that drug, would need to be submitted in full (i.e. not eligible under VGDS). Similarly, in a non-clinical setting, pharmacogenomic data generated and used as a screening methodology for potential pharmacologic or toxicologic activity to better select drug development candidates would be eligible for submission under VGDS.

?? The draft guidance provides a description of those circumstance that would constitute mandatory reporting to FDA of pharmacogenomic data and the expected level of detail to be submitted that is commensurate with the FDA biomarker category and the product registration status **[lines 284-293 and 343-375]**. It is suggested that the descriptions would be more helpful if specific (hypothetical) examples are included in order to illustrate the intent of the descriptions pertinent to non-clinical and clinical data submissions, dosing, efficacy, and safety.

?? We recommend that the guidance reflect that submission of full data sets generated with the microarray technology or SNP association study data is not expected if only an evaluation of a subset of genes is used for regulatory decision making. For example, when research is focused as the result of previous validation experiments, GSK would propose that it is more informative and appropriate that submission of data related only to the subset of genes of interest should be required.

?? The guidance does not address how the Review Divisions will respond to generated data (particularly exploratory data) and under what circumstances. It is requested that FDA outlines the mechanism for the Review Divisions to obtain appropriate (and timely) counsel and input from the IPRG and details safeguards to ensure that Review Divisions do not develop conflicting independent policy decisions. **[lines 498-509]**

?? What is the envisaged process, if any, in the event that there is disagreement between the sponsor and a Review Division regarding what is considered appropriate usage of the pharmacogenomic data? It is suggested that a process for resolving such differences, including the role of IPRG, be outlined in the guidance to facilitate consistency within Industry and across Review Divisions. **[lines 498-509]**

?? The guidance states that where a sponsor develops a drug for a selected population (safety considerations), co-development of an FDA-sanctioned IVD that is available when the drug is marketed, is required; however, where a sponsor is appropriately developing a drug for all-comers whilst also pursuing PG markers for toxicity, then the test could be available as an approved IVD or service.

It is requested that additional clarification be provided for the options highlighted in the draft guidance, recognizing that this may be more appropriately addressed in the 'co-development' guidance that FDA notes is to be available in the near future. **[lines 536-540 and 542-549]**

?? FDA has provided useful guidance regarding GLP data; however, GSK requests that this be expanded. For example, what guidance can FDA provide regarding the desired format / content for such data and what is required for validation? What is FDA's guidance for exploratory data that are generated within GLP non-clinical studies? Also, what is FDA's view regarding pharmacogenomic clinical data that are generated in research labs since these may not possess the same degree of rigorous sample handling / tracking and validated assay methodologies found in *clinical* laboratories. **[lines 393-405]**

?? It would be helpful if FDA provided more precise detail with regard to the scope and format for a full report vs. an abbreviated report vs. a synopsis, together with the conditions under which each is required. **[lines 111-113]**

?? The guidance does not address when FDA would advocate the generation of pharmacogenomic data. It would be helpful if FDA would describe scenarios and the process for incorporating utilization of "approved " biomarkers ("known valid biomarkers") for regulatory decision making into appropriate guidances, as for example, with regard to drug metabolism and CYP2D6. **[lines 106-119]**

VOLUNTARY PHARMACOGENOMIC DATA SUBMISSIONS

?? It is assumed that FDA intends for the sponsor to decide if available pharmacogenomic data fall within the scope of VGDS. What mechanism will be available for consulting with appropriate individuals at FDA regarding the respective sponsor and Agency views regarding such decisions? **[lines 223-242]**

?? There is a need for additional clarity for what FDA will and will not do with the data in VGDS and any assessments made. What is the contact with the Review Divisions and the intent for access to, and use of, the data by the Review Divisions? **[lines 489-509]**

?? Whilst FDA's flexibility regarding the format of data to be submitted under VGDS is welcomed, additional details specifying how much data should be included and what context is required would also be helpful. Also, what is the expectation of FDA for sponsors to meet with the IPRG regarding submitted data under VGDS? **[lines 410-434 and 498-502]**

?? Additional clarification is requested regarding what the 'triggers' could be for *"FDA becoming aware of the significance of a particular PG test after evaluating results across sponsors"* together with what the communication process is for *"notifying sponsors about this determination".* Combining different sets of VGDS data from different companies runs the risk of erroneous conclusions in addition to conferring significance to a dataset that was deemed initially to be of an exploratory nature – what does FDA envisage as a safeguard in this respect? **[lines 505-507]**

?? FDA is requested to provide additional details regarding the IPRG functioning - who sits on IPRG and will external members to FDA be eligible in a manner similar to the Advisory Committee concept (e.g. NIH, academia). GSK would encourage participation that provides 'state-of-the-art' input and counsel. **[lines 240-242]**

?? Based on the premise that confidentiality of the VGDS data needs to be maintained, how will this be achieved within the IPRG and how will potential conflicts of interest be managed? **[lines 236-242]**

?? GSK considers that information sharing is a critical component and incentive for industry with regard to the VGDS initiative. FDA is requested to outline the opportunities and process for this aspect regarding both an individual sponsor's data with IPRG as well as for 'cross-sponsor' data where a pattern of association might be identified by the IPRG. In the latter situation involving multiple sponsors, GSK supports discussion that is inclusive of all sponsors with the appropriate maintenance of sponsor proprietary information.