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VICE PRESIDENT
SCIENCE POLICY AND TECHNICAL AFFAIRS



February 2, 2004

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Re: Draft Guidance for Industry: Pharmacogenomic Data Submissions [Docket No. 2003D-0497, 68 *Federal Register*, 62461-62463, November 4, 2003]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

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit its comments to the Food and Drug Administration's (FDA's) *Draft Guidance for Industry: Pharmacogenomic Data Submissions* (Draft Guidance). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer and more productive lives. Investing more than \$30 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA welcomes and supports FDA's initiative to provide guidance on this complex and important topic. PhRMA member companies have worked closely with FDA to clarify how pharmacogenomic data can and should be used in drug development and Agency decision-making. PhRMA was pleased to have the opportunity to be a co-sponsor with FDA of the joint workshop organized by the Drug Information Association to discuss the draft guidance, which was held in Washington, D.C. on November 13 and 14, 2003. PhRMA's detailed comments on the draft guidance are set forth below.

I. Structure of the guidance

Before proceeding to a detailed review, we would like to comment briefly on the overall organization of the draft guidance. **We suggest** that the use of pharmacogenomic submissions relating to nonclinical, clinical pharmacology and clinical aspects of drug development should be considered in separate sections of the guidance because there are significant differences in the purposes, standards, processes, interpretation and impact of pharmacogenomic data in each of these areas. Alternatively, there should be at least a separation of nonclinical from clinical data submissions. It should be possible, in this way, to add detail, clarity and specificity to the guidance without extending it greatly. We request that FDA consider adding additional detail about the similarities and differences in pharmacogenomic data generated in the nonclinical and clinical settings.

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Pharmaceutical Research and Manufacturers of America

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II. Scope:

The draft guidance states (lines 31-33): *“Pharmacogenomics also does not refer to data resulting from proteomic or metabolomic techniques. This document is not meant to provide guidance on pharmacoproteomics or multiplexed protein analyte based technologies.”* The implications of this are that, at least for the time being, sponsors could not submit data from proteomic or metabolomic analyses and have them treated in the same way as data from genomic (DNA genotyping and RNA expression profiling) analyses, particularly with regard to the voluntary submission process. While we recognize that most results from the use of these technologies are still exploratory and that, therefore, there should generally be no requirement to submit proteomic and metabolomic data to INDs, NDAs and BLAs, we believe that there will be situations when it will be no less useful to a sponsor to be able to submit proteomic or metabolomic data under the voluntary process than it is to submit genomic data. **We recommend** that FDA reconsider the scope of the guidance to include the voluntary submission of data from any of the genomic, proteomic or metabolomic technologies.

III. “Decision-making” and “regulatory decision-making”

The phrases above are used repeatedly throughout the draft guidance, without a clear definition of either of them. We believe that there is an important difference between them that merits their separate definition. **We suggest** that “decision-making,” in this context, should be defined as *“the use of pharmacogenomic and other data by a sponsor to select a solution, design or strategy during drug development.”* “Regulatory decision-making” should be defined as *“the use of pharmacogenomic and other data by a regulatory authority to support determinations under applicable regulatory standards with respect to a clinical trial application or protocol or a marketing application for a drug, including the conditions (e.g., labeling) under which the drug should be used.”*

IV. Nature and Use of Pharmacogenomic Data

According to the algorithm in Appendix A, data required for clinical decision making or to provide scientific rationale must be provided in full. However, sponsors might consider this data to be exploratory and, therefore, eligible for VGDS. Also, the requirement for submission of any analysis on a known valid biomarker, regardless of association, is higher than that of other biomarkers. **We recommend** that a distinction be made between pharmacogenomic results that drive decisions in a single clinical trial and those that drive decisions in a clinical development program. In a clinical trial, if genotype is used to screen or select subjects, or to stratify the primary analysis, those results should be reported. On the other hand, if retrospective pharmacogenomic analysis of one clinical trial leads a sponsor to make decisions about the design of subsequent trials, those data should be eligible for a Voluntary Genomic Data Submission (VGDS) if they are exploratory in nature and do not contribute to the evaluation of the safety or efficacy of the drug.

In the algorithms for data submission, the decision points would be clearer if they were based solely on how the data would be used rather than whether a related biomarker is “known” or “probable.” Any data not used to make a claim for a drug, or to

support a scientific position, is exploratory research that would qualify for voluntary submission of a full report to an Investigation New Drug application (IND), or of a synopsis to a New Drug Application (NDA) or Biologics License Application (BLA). Pharmacogenomic data can be used for screening, selection, mechanistic and stratification purposes. **We suggest** the following definitions:

- ❖ Screening: Use of genotype or gene expression profile to investigate, in a predictive mode, the potential pharmacologic or toxicologic characteristics of experimental compounds in the discovery process in order to select the best development candidates. Screening data would generally not be submitted.
- ❖ Selection: Use of genotype or gene expression profile as inclusion or exclusion criteria or to assign potential subjects to different arms of a trial, for example to receive different doses if randomized to an experimental agent. Selection may, or may not, be balanced. These data would be submitted to the IND or NDA/BLA.
- ❖ Mechanistic: Use of genotype or gene expression profile to investigate the biological mechanisms giving rise to the pharmacologic, pharmacokinetic or toxicologic characteristics of a compound in a non-clinical or clinical setting. These data would generally be submitted to the IND or NDA/BLA.
- ❖ Stratification: Use of genotype or gene expression profile as a covariate or factor in analysis of a clinical trial. For example, in a trial the primary efficacy analysis may be limited to subjects having a certain genotype, whereas all subjects are included in safety analysis. Pharmacogenomic data used for stratified primary analyses are material to the regulatory evaluation of the drug and, therefore, should be submitted to the NDA/BLA, but stratified secondary or exploratory analyses should be eligible for VGDS.

Finally, submission of full data sets generated in microarrays or single nucleotide polymorphism association studies is **not recommended** if only a subset of genes is used by investigators to make their interpretation based on previous validation experiments. In such situations, submission of data related to this subset of genes is considered more efficient and informative.

V. Biomarkers

The draft guidance defines a “biomarker,” a “valid biomarker” and two subspecies, a “known valid biomarker” and a “probable valid biomarker.” We feel this is confusing, and that the same distinctions could be accomplished more simply. However, we believe that the primary issue is not the definition of biomarkers of different degrees of “validity,” but the process by which a biomarker would be accepted as an authentic basis for particular regulatory decisions.

We propose the following definitions:

- ❖ *Biological marker* (biomarker) – a characteristic that is measured objectively and evaluated as an indicator of normal physiological processes, pathological processes or pharmacological responses to a therapeutic intervention.
- ❖ *Established biomarker* – a biomarker that is measured in an analytical test system with externally¹ validated performance characteristics and for which there is a compelling scientific framework or body of evidence that elucidates the biological significance of the test results, and that has been publicly established through the work of multiple investigators. [For purposes of regulatory decision-making, an established biomarker is one that the regulatory authority either has accepted as authentic in the past, or commits to accepting as authentic for the future (see text below).]
- ❖ *Emergent biomarker* - a biomarker that is measured in an analytical test system with externally validated performance characteristics and for which there appears to be a coherent scientific framework or body of evidence that elucidates the biological significance of the test results.

In this scheme, there is no “valid biomarker,” because an “invalid biomarker” would be meaningless, and the “known valid biomarker” and the “probable valid biomarker” of the draft guidance are replaced by the “established biomarker” and the “emergent biomarker,” respectively.

The draft guidance proposes the distinctions between “emergent” and “established” biomarkers, but does not define a process for the former to be recognized as the latter for the purposes of regulatory decision-making. This recognition is, clearly, of critical concern to drug sponsors. The issue is not the extent to which a biomarker has been well supported by evidence and, perhaps, adopted or endorsed by one or more expert groups but, specifically, whether FDA either has used, or will commit to recognize, the biomarker for regulatory decision-making. In practice, only FDA can make a final decision to accept or reject a specific biomarker for regulatory decision-making in a particular context, so the Agency’s acceptance will become the *de facto* definition of an “established” biomarker for this narrow purpose. It is entirely conceivable that a biomarker could be apparently well supported by evidence and endorsed by other groups or institutions, but not be accepted by FDA for regulatory purposes. In this sense, the attempts to define “probable valid” (“emergent”) and “known valid” (“established”) biomarkers are redundant.

Therefore, **we recommend** that:

- a) FDA should define a process by which sponsors could prospectively gain a commitment that a particular biomarker would be accepted for regulatory decision-making. The process description should include a list of the data

¹ “Externally,” in this context, means “by reference to independent and objective measures of activity or presence.”

elements that sponsors could use in assembling their submission relating to an emergent biomarker, or an algorithm by which the sponsor could assemble his data into a construct that FDA would find persuasive. It is recognized that the circumstances in which a particular characteristic might be acceptable for regulatory decision-making would be limited to a subset of its overall occurrence as a biological phenomenon – these limitations should also be described. The guidance should also discuss the concept that some of the most predictive biomarkers are patterns or signatures (of either single nucleotide polymorphisms or gene expressions), rather than (collections of) individual markers. For example, it is generally established that the confidence in classifications based on gene expression patterns is enhanced when the patterns comprise larger numbers of genes, with the presence or absence of any individual gene usually having little or no effect on the classification. In proposing new signatures for regulatory decision-making, it should be accepted that sponsors should validate the pattern, rather than the individual elements within it, and general guidance should be given as to how to do this, and how to report it.

- b) Ideally, the definition of this process should be included in the final guidance on Pharmacogenomic Data Submissions, but we recognize that defining this process might take longer than the Agency would wish to spend before finalizing the current draft. In that case, the definition of a process for establishing biomarkers should be the subject of another guidance at the earliest possible time.
- c) In addition, FDA should publish a list of all the pharmacogenomic biomarkers that it has already accepted, or would be prepared to accept, for regulatory decision-making with the contextual background for each, so that sponsors can regard these biomarkers as “established” or precedented. The list should be updated as additional biomarkers are accepted for regulatory decision-making.
- d) According to the draft guidance, pharmacogenomic data on all “known valid” and “probable valid” biomarkers that are submitted to support aspects of the safety or efficacy evaluation of a drug must be submitted in full. However, in establishing “known” biomarkers for regulatory decision-making, FDA should be careful to recognize and define the limitations of its determinations – it should not be assumed that a particular characteristic will necessarily function as a reliable biomarker in all contexts. Hence, a “known valid” biomarker in one context will usually be an exploratory biomarker in other circumstances. This concept has important consequences for the interpretation of the guidance. For example, lines 356-362 (and lines 708-711) state that pharmacogenomic data on “known” biomarkers, upon which the sponsor is not relying, should be submitted in abbreviated reports. We submit that, in practice, it will be important to distinguish between biomarkers that are being used in the context in which they were found to be authentic, and biomarkers that have been found to be authentic in some circumstances, but are being

used by the sponsor in a different context. We accept that, in the former case, the data should be submitted under 21 CFR 314.50 and 21 CFR 601.2. However, in the latter case, we consider that the data do not relate to either “known” or “probable” biomarkers, but are actually the results of exploratory research. As such, and following the logic of the guidance (see, e.g., lines 301-302), **we contend** that they are not required to be submitted to an IND but may be submitted as a VGDS at the sponsor’s discretion. **We recommend** that the guidance should clarify this point.

- e) The guidance should also clarify whether the availability of an approved In Vitro Diagnostic (IVD) or CLIA² test is relevant to the determination that a biomarker is a “known valid biomarker” (“established biomarker”) for regulatory decision-making.

VI. General issues for mandatory data submission

We recommend that the guidance should address the following issues related to mandatory submissions of pharmacogenomic data.

- a) Clarification of general principles

We recommend that the following language be added for clarification at line 120: *“When an IND or NDA/BLA application is submitted for review or is approved, pharmacogenomic studies are required to be reported either as synopses, abbreviated reports or full reports, depending on the use of the data in the submission. Exploratory data may be submitted voluntarily as a full report to the IND at any time during the investigational phase, or to the NDA/BLA at the time of application or in annual updates.”*

- b) Quantity of data to be submitted

Pharmacogenomic technologies often generate exceptionally copious quantities of data on genes and their expression, whether or not the functional relevance of the genes is known. To reduce the amount of work required by the sponsor in submitting data and to avoid overburdening the FDA with irrelevant data files, **we recommend** that the guidance should indicate that it is for the sponsor to decide, at least initially, what data sets are relevant for submission.

- c) Data quality

There is little guidance on the quality and quality control of pharmacogenomic data that may be submitted in connection with regulated studies, although it is stated that nonclinical data should be compliant with 21 CFR Part 58 (lines 402-403). Sponsors generally seek to submit data of the highest possible quality; however, clinical data may be generated using different standards or using a variety of different assay

² Clinical Laboratory Improvement Amendments.

formats, e.g., homebrews, non-CLIA validated assays, IVDs, etc. Therefore, **we suggest** that it should be stated that it is the sponsor's responsibility to conduct appropriate quality control of data. Pharmacogenomic data used to support clinical drug development for regulatory purposes should not be required to be of a higher standard than any other assays used in clinical trials.

d) Negative data

It is desirable that negative data about "known valid biomarkers" ("established biomarkers") be submitted to INDs, NDAs, and BLAs.

e) Compliance with other guidelines

The section of the guidance on data submission (Section IV, p.6) should indicate how to submit the different types of reports of pharmacogenomic studies within the context of other texts relating to the desired structures for regulatory submissions, particularly those relating to electronic submissions, annual reports and to the Common Technical Document (CTD) agreed under the International Conference on Harmonization.

f) Abbreviated reports and synopses

The draft guidance states (lines 111-113) that sponsors should refer to FDA's guidance on Abbreviated Reports and Synopses³ for further information on when these types of reports may be submitted. However, while the latter guidance is helpful, it does not address some of the circumstances in which pharmacogenomic data may be submitted under the current draft guidance (e.g., nonclinical studies). The 1999 guidance describes in detail the circumstances in which abbreviated or synoptic reports may be submitted for each of the types of studies considered, and lists the data elements, and their organization, that should be included in an abbreviated report. Again, these formats are conceptually helpful, but are not necessarily directly relevant to reports of pharmacogenomic studies. The draft guidance states that other guidances will be forthcoming that will make recommendations on data formats for submissions to INDs, NDAs and BLAs. However, rather than having this information in a range of separate guidances, **we recommend** that, within the guidance on Pharmacogenomic Data Submissions, FDA develops the section on data submissions to include detailed outlines for submission of pharmacogenomic data in Full, Abbreviated or Synoptic reports of nonclinical, clinical pharmacological or clinical reports, for both genotyping and expression data, analogous to the treatments used in the 1999 guidance.

³ Guidance for Industry: Submission of Abbreviated Reports and Synopses in Support of Marketing Applications; Food and Drug Administration, August, 1999.

VII. Voluntary genomic data submissions (VGDS)

In the draft guidance, FDA requests that sponsors consider the voluntary submission of certain categories of exploratory or research pharmacogenomic data that are not required to be submitted under the IND, NDA or BLA regulations (lines 221-242). **We recommend** that many aspects of the process and conditions for VGDS be described in greater detail.

a) Interdisciplinary Pharmacogenomic Review Group (IPRG)

- i. What will be the composition (expertises represented, affiliations, etc.) and terms of reference of the IPRG? For some of the functions ascribed to the IPRG in the draft guidance (lines 240-242), we believe that there would be advantages to constituting an advisory committee under the Federal Advisory Committee Act of 1972 and 21 CFR Part 14, in that it could include government, academic and, possibly, industrial representation. We believe that this would ensure the highest levels of expertise and transparency, and that this type of body would be ideal for the horizontal review of accumulated data across many drugs, advising FDA as to the authenticity of pharmacogenomic biomarkers for regulatory decision-making (see Section V above) and proposing new guidance and policy in this area. Moreover, it is not clear to us that, due to the highly technical nature of much of pharmacogenomics, these functions could be assumed readily by any of FDA's existing advisory committees. We could envisage such an advisory committee working in tandem with an IPRG constituted from within FDA.

We realize that it would also be possible to arrange for expert consultations between agency staff, academic experts and industry representatives by other means (e.g., by arranging periodic *ad hoc* public workshops). However, we believe that a formally constituted advisory committee would be preferable because it could more easily maintain a consistent membership, establish operational definitions and conventions, liaise with the IPRG and plan a program of work extending into the medium term (e.g., 6-18 months).

- ii. **We expect** that VGDS submissions will receive the same confidentiality as do drug approval applications to FDA. Since the VGDSs will be reviewed by the IPRG as well as the relevant review division, **we recommend** that FDA should give more information in the guidance about how the confidentiality of VGDS submissions will be ensured, and any conflicts of interest managed, if the membership of the IPRG includes those who are not employees of FDA⁴ or who may not be accustomed to working under the strict confidentiality imposed by FDA's review divisions.

⁴ There has been informal discussion of, for example, staff of the National Institutes of Health being involved in the IPRG.

- iii. Will the IPRG come to binding decisions or make recommendations with respect to an individual sponsor's data or analytical methods? If so, what opportunities and process will be put in place for the sponsor to discuss these with the IPRG? We regard it as critical that sponsors should have opportunities to receive and discuss information about new signals or signatures ("emergent biomarkers") identified by the IPRG. These could be identified in an individual sponsor's data, in which case the discussion with IPRG should probably (but not necessarily in every case) be restricted to that sponsor for reasons of confidentiality but, perhaps more typically, patterns of associations might be identified across submissions from multiple sponsors, in which case the discussion should be open to all sponsors. We feel that this information sharing is an important incentive for industry to participate in the VGDS initiative and that the guidance should contain descriptive language.
- iv. What will be the relationship between the IPRG and the FDA review divisions? The draft guidance states (lines 499-500) that "*VGDS filings will be analyzed by the [IPRG] and the relevant review division staff,*" but this does not clarify whether the review division staff will conduct their analysis independently of the IPRG or will effectively become members of the IPRG for that discussion. Since VGDS submissions will be reviewed by both groups, what will be their respective and complementary roles?
- v. Does the statement that the IPRG will be concerned with the review of VGDSs (see ii. above) imply that this group will not be involved in the review of pharmacogenomic data mandatorily submitted to an IND, NDA or BLA? If the IPRG will be involved, even in a consultant capacity, with the review of pharmacogenomic data to regulated applications under certain circumstances, these circumstances should be described fully in the guidance.
- vi. Will there be circumstances in which the IPRG will be able to recommend that data that were submitted voluntarily (or later versions of the same data) be also submitted as part of a regulated submission? The draft guidance is not clear on this point: it states, "*The FDA will not use information submitted through the voluntary process for regulatory decision making on INDs or NDAs.*" (lines 498-499), but then, "*However, after the sponsor submits a VGDS, if additional information becomes available that renders the results required to be submitted ..., the sponsor must submit the data to the IND, NDA or BLA ...*" (lines 503-505). It is not clear whether the "*additional information*" is intended to mean information relating to the sponsor's own drug (in which case it would be expected that he would know about and understand the significance of the later data)

or information derived from, for instance, horizontal analyses of data from several sponsors' drugs (in which case any single sponsor could not be expected to know about the other sponsors' data, or their significance for the submission for regulatory decision-making of his own data, previously submitted voluntarily.) Particularly if the information, whose discovery could result in a sponsor having to submit to a regulated submission data that had been previously submitted voluntarily, could come from horizontal analyses of data from several sponsors, sponsors could be faced with significant regulatory risk as a result of the voluntary submission of data in good faith. This conclusion is completely at odds with the spirit of the VGDS process, as stated, that FDA will not use voluntarily submitted data for decision-making. It is very important for sponsors that they are able to understand and control any regulatory risk involved in making a VGDS submission since this is a voluntary process.

Therefore, **we recommend** that FDA clarify in detail the circumstances under which a mandatory submission for regulatory decision-making of voluntarily submitted data would be justified and also describe what dispute resolution procedures would be open to affected sponsors in the event that they might disagree with FDA's judgment in these matters.

b) Value of VGDS to sponsors

The value to sponsors of using the VGDS process is not clearly stated in the draft guidance, beyond the assertion that the submission of data under VGDS will help to educate Agency staff as to how pharmacogenomic techniques are being used in drug development. While we strongly support FDA in its efforts to keep its staff aware of new technological approaches, we believe that there should be more concrete and specific benefits for the individual sponsor, who may expend considerable resource in preparing a voluntary submission. A benefit that would attract sponsors would be an opportunity to discuss the data with the review division/IPRG, with a view to reducing some aspects of the regulatory risk in the development of the drug in question, or of leveraging its development in some other way, although we recognize that this would not apply for every VGDS. **We recommend** that the value of VGDS to sponsors should be addressed in a separate section of the guidance, and that a process for discussion of the data with the review division/IPRG should be defined. Ideally, the discussion could be integrated with other routine meetings between sponsors and the Agency e.g., pre-IND meetings or end of Phase II meetings, etc., if the VGDS related closely to the drug development project under discussion, but there should also be a possibility for sponsors to discuss their pharmacogenomic data and strategies with relevant groups within FDA (the review division and/or the IPRG) outside the routine regulatory milestone meetings.

- c) Fate of data and analyses accumulated from VGDS submissions
FDA has indicated in the draft guidance that it intends “to develop an aggregate genomic knowledge database from multiple VGDSs that could be used to rationally facilitate the use of pharmacogenomics in drug development and to share what general knowledge is learned from the data repositories, where appropriate.” (Lines 421-424). **We suggest** that the guidance should go further to describe how individual sponsors’ data will be entered into the database with respect to allowing users of the database to associate data with specific drugs and sponsors. How will the database be designed to accommodate data of different types and in different formats? Under what circumstances, if any, will FDA make the database accessible to researchers outside the Agency/IPRG? Sponsors might wish to submit their data for analysis and discussion with the IPRG, but not to have them included in the database – would they have an option to request this exclusion?
- d) Reports of microarray experiments
Lines 428-467 - While the draft guidance describes three examples of the proper format for submitting VGDS data to FDA, it does not recommend a specific format. However, it does indicate that the submission needs to contain a sufficient level of detail for FDA to independently analyze the data, verify the results, and explore correlations across studies. **We recommend** that FDA provide more specific detail regarding the approaches that it will take in analyzing and verifying the data. Depending on the analytical approaches used by the Agency, the descriptive journal format example may not be sufficient. We support the descriptive submission of the relevant data, or in cases where an entire dataset must be submitted, the MIAME format. The third example listing is very inclusive and may not represent the least burdensome approach.
- Lines 441-467 indicate that all data on all genes should be included in the report. FDA should assure that data submitted under VGDS will not be used to determine other clinical associations with genes already known as biomarkers or genes that will become known biomarkers in the future. While lines 458-460 cover the validation of gene expression data by “conventional technologies,” **we recommend** that validation of expression profiles, gene by gene using RT-PCR or Northern assays, for example, should not be required or recommended. In many situations, the expression results may be a pattern of genes that is diagnostic or prognostic and not amenable to validating every gene in the signature.

VIII. Compliance with 21 CFR Part 58

Section IV. D of the guidance (lines 391 – 405) concludes that, “the requirements of part 58 apply to nonclinical studies submitted to support safety findings, including nonclinical pharmacogenomic studies intended to support regulatory

decisionmaking". However, there are several obstacles to making pharmacogenomic analyses GLP-compliant. Firstly, the technologies that are used to generate pharmacogenomic data are varied and complex and will be inherently difficult to validate. Secondly, pharmacogenomic analyses are not routinely included in toxicology studies and, therefore, it may be difficult and costly for the sponsor to create the facilities and infrastructure required to generate GLP-compliant pharmacogenomic data. Thirdly, at the present time there is no consensus between the industry and FDA as to what constitutes a GLP regime for some pharmacogenomic technologies. Therefore, in order to give sponsors the greatest flexibility in generating pharmacogenomic data from toxicology studies and to maximize the amount of pharmacogenomic data that are available to the FDA, we propose that pharmacogenomic data, in large part, be treated similarly to other bioanalytical or pharmacodynamic data that are exploratory in nature, or for which significant impediments exist to making such data compliant with Part 58.

Therefore, **we suggest** that the following additional text be inserted in the guidance: "*Pharmacogenomic analytical techniques may not readily lend themselves to full compliance with Part 58 due to their complex nature and difficulties in creating Part 58 compliant laboratories. Therefore, it may not be feasible for the Sponsor to comply completely with Part 58 for pharmacogenomic nonclinical studies. In these instances, the Sponsor will clearly indicate in the study report the areas in which such data do not comply with Part 58 and the rationale for the non-compliance. Such data can still be used in the interpretation of safety findings in nonclinical studies as long as the data can be supported by a strong scientific rationale and evidence of the sponsor's due diligence. For pivotal nonclinical studies, the Sponsor should make all reasonable efforts to comply with Part 58.*

To facilitate the use of exploratory pharmacogenomic research to understand the mechanisms of action and safety of compounds at the nonclinical stage, **we recommend** that FDA add a section to the guidance that specifically addresses the collection and storage of samples from animal and *in vitro* studies conducted under Good Laboratory Practice (GLP) for future undefined or defined pharmacogenomic research.

- ❖ Exploratory pharmacogenomic research should not necessarily have to be performed under GLP conditions on samples collected from animal studies conducted under GLP.
- ❖ *In vivo* and *in vitro* toxicity studies conducted under GLP should allow sponsors an option for either the collection and storage of additional samples or the ability to store and use residual samples, for exploratory pharmacogenomic research. The collection, storage and analysis of cells, organs or tissues from *in vitro* or *in vivo* GLP studies for this research will be specified within or appended to the study protocol as non-GLP procedures, and will be reported as a report amendment to, or separate report from, the customary GLP analyses.
- ❖ The sponsor recognizes that data generated from pharmacogenomic studies (not exploratory studies) conducted on samples collected from

animal studies conducted under GLP would be submitted to INDs, NDAs and BLAs, as stated in the draft guidance.

IX. Harmonization

We believe that, with the VGDS process, FDA has created a potentially powerful system that could yield important benefits, both in terms of understanding the significance of specific pharmacogenomic biomarkers in drug development and in applying pharmacogenomic knowledge to the regulation of drugs. **We recommend** that FDA should discuss this approach with international regulatory authorities, especially those in Canada, the European Union and Japan, so that equivalent or cooperative systems could be established in those territories. We would be keen to work with FDA and the other relevant parties to establish a consensus approach, based on the current guidance, within the framework of ICH.

X. Miscellaneous and typographical points

- a) The draft guidance is addressed to “*Industry*” but, in reality, will also guide FDA review staff and members of the Interdisciplinary Pharmacogenomic Review Group (IPRG). In the interests of completeness and of encouraging all concerned to work strictly from the same premises, we suggest that the document be entitled, “*Guidance for Industry, FDA Reviewers and Interdisciplinary Pharmacogenomic Review Groups: ...*”. We realize that this might be considered slightly redundant, in that guidance documents are described as “*...documents prepared for FDA staff, applicants/sponsors, and the public...*”⁵, but we feel that any redundancy would be justified on this occasion.
- b) Line 62-63 – We recommend not describing pharmacogenomics as “*relatively new*”. We suggest beginning the sentence, “*At the time of writing, most experimental results from pharmacogenomics may not be well enough established....*”
- c) Lines 299, 461 and others - The specific term “*single nucleotide polymorphism (SNP)*” should not be used when the generic term “*polymorphism*” is correct.
- d) Line 461 - Double-stranded DNA sequencing, not single-strand conformation polymorphism (SSCP), should be the reference standard for validation of polymorphism assays.
- e) Lines 581-589 - “*Pharmacogenomic tests*” should be defined independently of sequence variation – that is, the definition should comprise gene expression and epigenetic tests, whereas “*pharmacogenetic*”

⁵ 21 CFR 10.115(b)(1)

tests” should comprise variations in DNA sequence (either candidate gene or whole genome).

- f) Line 591 - FDA’s glossary definition of “Valid Biomarker” is inconsistent with the definition developed by the Biomarkers Definition Working Group (BDWG), upon which the FDA definition is based. In particular, the BDWG has asserted, “*validation is unsuitable for the description of the process of linking biomarkers to clinical endpoints...*”⁶ This further underscores the need for FDA to define those biomarkers that may be used for regulatory decision-making and to revise the glossary to clarify this point.
- g) Lines 753-759 - The use of pharmacogenomics to define ethnicity-specific dosing regimens should not be encouraged by including an example of this. Race and ethnicity are social concepts lacking scientific relevance. The presence of an association between race/ethnicity and drug response should be interpreted only as an indication that some important factor/covariate, either genetic or environmental, remains unobserved.
- h) Lines 779, 786: We suggest using either the HGP gene name *ABCB1* (preferred) or the commonly used *MDR-1*.
- i) Examples should be added related to physiologic genes e.g., relation of *F5* genotype to prothrombin time in clinical trials of a new oral contraceptive.
- j) Line 651 - In the algorithm for IND submission, the phrase “*in an animal trial used to support safety*” is vague. We suggest the following: “*in a pivotal toxicologic study to support the safe design or conduct of clinical trials . . .*”
- k) Lines 206, 219 – the abbreviation “IDE” (Investigational Device Exemption) should be defined.
- l) Line 851 – The section number “IV.B.2” should be changed to “IV.A.2.”
- m) A growing number of pharmacoepidemiologic studies are being conducted to investigate safety concerns of drugs identified in post-marketing adverse event reports. An important part of the objectives for these studies has often been the identification of risk factors or high-risk subpopulations. Genotypes or gene expression profiles are often studied as potential risk factors along with other variables such as age, gender, race, co-morbidity, and co-medications. Therefore, it would be useful to provide some guidance on how the pharmacogenomic data collected in pharmacoepidemiologic studies would be submitted to or used by the FDA. Additionally, how would FDA review pharmacogenomic data

⁶ Clinical Pharmacology & Therapeutics (2001) Vol. 69, p. 93.

collected from observational, non-interventional studies, when they are not associated with a drug, either investigational or approved?

We commend FDA again for its leadership in establishing a regulatory pathway for the submission of pharmacogenomic data. We appreciate the opportunity to comment on the draft guidance and look forward to working with FDA to implement the guidance and to integrate pharmacogenomics fully into drug development for the benefit of patients.

Sincerely,



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