



Date: JAN 21 2004

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

2004 JAN 22 10:14

Re: Docket No. 2003D-0497
Response to FDA Call for Comments
Draft Guidance for Industry: Pharmacogenomic Data Submissions

Dear Sir or Madam:

Reference is made to the November 4, 2003 Federal Register notice announcing the request for comments on Docket No. 2003D-0497 entitled Draft Guidance for Industry: Pharmacogenomic Data Submissions.

AstraZeneca has reviewed this draft guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to Gregory Taylor, Regulatory Project Manager, at (302) 886-1216.

Sincerely,

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Regulatory Affairs
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Enclosure

2003D-0497

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US Regulatory Affairs
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Docket No. 2003D-0497

Draft Guidance for Industry on Pharmacogenomic Data Submissions

General Comments

- Comment 1

AstraZeneca (AZ) regards the production of this document as a very positive step in drug development and the start of a process that will enable more pharmacogenetic and pharmacogenomic (PG) data to be generated and submitted to support the development of safer, more effective drugs. In addition, AZ appreciates the effort FDA is making to consult on this guidance and the willingness expressed at the recent DIA meeting on this guidance to make revisions based on the comments received. In general the guidance is constructive in trying to assist the sponsor in complying with the regulations whilst offering the opportunity for the sponsor to have discussions on exploratory markers outside the IND and NDA process.

- Comment 2

AZ believes that further clarity is needed to address the concerns already recognized by the FDA. For instance, the guidance recognizes 'the concern that the Agency will raise new questions and require additional data based on findings from exploratory pharmacogenomic studies, that new studies will be required or suggested based on preliminary human pharmacogenomic data, that indicated populations will be narrowed or restricted based on the pharmacogenomic results in subpopulations, or that new studies in subpopulations will be required after retrospective analysis suggests differential responses based on pharmacogenomic subgrouping'. However, these concerns are not answered explicitly in the present document. Further clarity on these questions would help reassure the pharmaceutical industry about the use of PG data. The key areas where further consideration is required are listed below and addressed in the more detailed line listing section of this document:

- Clarification of marker status and how it will be assigned
- Confidentiality of VGDS data and the impact of one sponsor's data on another
- How FDA will use VGDS data and the level of detail requested
- The need for a global alignment on PG guidance
- More definition on how to handle pivotal studies including exploratory endpoints

- Comment 3

The voluntary genomic data submission (VGDS) process is an important innovation that should significantly increase the amount of PG data submitted to the FDA. In order to maximize this increase, AZ believes it is essential that the sponsor should take responsibility for both the decision of whether to submit data by this route and the format of the submission. In particular, it may not always be appropriate to submit raw genetic data to the FDA, because of the perceived sensitivity of genetic data, and compliance with other regulations such as HIPAA.

- Comment 4

AZ welcomes the general approach of defining PG markers as biomarkers, although AZ would find clearer definitions of the different types of biomarkers helpful. However, it may be more important to agree the process by which new biomarkers are defined into their various categories. Given the difficulty of reaching consensus in this field, and the implications of this decision, AZ recommends a process that is transparent and respected by all parties, and potentially similar to the process utilized by the Carcinogenicity Advisory Committee for a carcinogenicity protocol review.

- Comment 5

AZ supports FDA's ambition in creating the guidance and enabling sponsors to obtain drug approval in a faster and more effective fashion utilizing PG data. AZ recommends a sponsor have the opportunity to demonstrate to FDA that a biomarker (used as primary or supportive data in a pivotal study) is robust and adequate to support the approval of a marketing application, regardless of publication status. It will be essential to discuss and approve early in the drug development process the biomarker validation plan for which the biomarker will be used to support a marketing application. In addition, the sponsor in collaboration with the FDA should have the option of utilizing a probable valid biomarker for pivotal data in a development program.

- Comment 6

AZ believes it may simplify future communication to address non-clinical submissions and clinical submissions separately in future drafts.

- Comment 7

In terms of confidentiality of VGDS data, assurance needs to be clearly provided that this will be respected. The data should be held to the same confidential level afforded by the applicable regulations and laws currently effective at the time the sponsor submit data to the FDA.

- Comment 8

The IPRG (Interdisciplinary Pharmacogenomic Review Group) will serve as a critical function in working with sponsors throughout the process. Further clarification and definition regarding the membership of this group, their interaction with divisional reviewers, and their role in increasing knowledge with academia is necessary. AZ recommends the IPRG is an unbiased group of individuals in order to protect sponsor's intellectual propriety rights.

- Comment 9

A critical component of the guidance will be collaboration between FDA and the sponsor. The guidance should be clear that there would be the opportunity for sponsors to meet with FDA to discuss the opportunities the data might offer and meetings should be available within a reasonable time frame to discuss the impact on the development process. Delays to the interactive process will negatively impact the ability for industry to participate.

- Comment 10

Consideration needs to be given to ensure that there will not be different data requirements globally as this would impose a significant burden on sponsors thereby reducing the beneficial effect of this initiative. AstraZeneca recommends early and consistent communications/interaction between key health authorities e.g. United States, Europe and Japan. AZ also recommends that there is an effort made for different health authorities to use common terminology and definitions. As an example, the terms used by the FDA are not consistent with the standard terms defined by the EMEA in December 2001.

- Comment 11

A point not addressed in the guidance is the level of detail expected in the labeling in relation to any diagnostic that is required as part of the effective administration of the drug. In order to avoid numerous changes to the drug labeling there should be recognition that the information included vs. the diagnostic should be minimal. If this is not the case there will inevitably be large numbers of labeling changes in this fast moving area. This will present a burden to both industry and to health authorities that would need to review the label.

Section	Page or Line Number	Comment or proposed replacement text
II. Background	Line 50	AZ recommends that consideration needs to be given to ensure that there will not be different data requirements globally as this would impose a significant burden on sponsors thereby reducing the beneficial effect of this initiative. AZ also recommends early and consistent communications/interaction between key health authorities e.g. FDA, Europe and Japan are required. There should be an effort made for different health authorities to use common terminology and definitions. The terms used by the FDA are not consistent with the standard terms defined by the EMEA in December 2001.
II. Background	Line 80	The document needs to clarify use of data in “decision-making”.
III. Submission Policy A. General Principles	Line 128 – 156	<p>There is a lack of clarity as to who makes the decision that a PG test is a valid biomarker. Should FDA wish to publish a list of valid biomarkers there should still be a mechanism for sponsors to demonstrate that a PG test not currently on the list is valid, irrespective of whether they are the sole generator of data to support its validation.</p> <p>AZ recommends a sponsor have the opportunity to demonstrate to FDA that a biomarker (used as primary or supportive data in a pivotal study) is robust and adequate to support the approval of a marketing application, regardless of publication status. It will be essential to discuss and approve early in the drug development process the biomarker validation plan for which the biomarker will be used to support a marketing application. In addition, the sponsor in collaboration with the FDA should have the option of utilizing a probable valid biomarker for pivotal data in a development program.</p> <p>Consideration needs to be given as to how markers may transition between “exploratory”, “probably known” and “valid” and the impact such transitions might have on other sponsors.</p> <p>There needs to be the opportunity for a sponsor who has a pharmacogenomic test with appropriate data generated to use this as pivotal data to aid speed of drug development.</p>
III. Submission Policy A. General Principles	Line 136-141	AZ recommends clarifying how the PG data is classified if it is a combination of a known valid biomarker plus a probable valid biomarker impacting on one clinical phenotype. For this example, AZ recommends that it should (all) be considered as a probable valid biomarker because the clinical significance of the PG data as a whole is not known. In the case where different categories of markers impact different phenotypes, AZ recommends there could be separate submissions according to the algorithm in the guidance document.

Section	Page or Line Number	Comment or proposed replacement text
III. Submission Policy B. Specific uses of PG Data in Drug Development and Labeling	Lines 169 – 175	AZ recommends that the criteria for regulatory decision-making needs to be explicitly stated in the relevant study protocol.
III. Submission Policy B. Specific uses of PG Data in Drug Development and Labeling	Lines 181 – 193	The guidance implies it is possible to refer in prescribing information to tests that are not commercially available or FDA approved. AZ is requesting FDA to clarify if this is the intended purpose of this wording and provide examples.
III. Submission Policy B. Specific uses of PG Data in Drug Development and Labeling	Lines 195 – 219	AZ is requesting confirmation that it is not essential for diagnostics to be FDA approved.
C. Voluntary Submission of Exploratory Pharmacogenomic Research Data	Line 240	AZ recommends further clarity regarding the staffing of the IPRG (Interdisciplinary Pharmacogenomic Review Group) in terms of the membership, confidentiality, and timeliness to responses of meeting requests and data submissions.
IV. Submission of PG Data A. Submission of PG Data During the IND Phase	Lines 274 – 276	AZ is requesting clarification regarding the reference to “validity”. Tests validated by a single sponsor should be able to support regulatory decision-making.
IV. Submission of PG Data A. Submission of PG Data During the IND Phase	Line 289	AZ recommends that the sponsor be able to justify the classification of a biomarker as a known validated biomarker or purely exploratory. This is particularly critical in cases where there is extensive literature about the biomarker in question, but it is equivocal and experts disagree on its interpretation.
IV. Submission of PG Data	Line 292	The marker status even of CYP2D6 depends on the alleles tested. Some alleles have no known clinical relevance or the relevance is

Section	Page or Line Number	Comment or proposed replacement text
A. Submission of PG Data During the IND Phase		different for different drugs. Further clarification versus such situations would be helpful.
IV. Submission of PG Data A. Submission of PG Data During the IND Phase	Line 299	Replacement text: Anonymous SNP.
IV. Submission of PG Data A. Submission of PG Data During the IND Phase	Line 311	Delete 'submission' (redundant after VGDS).
IV. Submission of PG Data A. Submission of PG Data During the IND Phase	Lines 311 – 315	Clarity is necessary to address the potential scenario if another sponsor validates a biomarker or a biomarker becomes validated during a drug development program.
IV. Submission of PG Data B. Submission of PG Data to a New NDA, BLA or Supplement	Lines 368 – 375	AZ is requesting confirmation that it is acceptable to include exploratory biomarker tests in pivotal protocols (clinical and non-clinical). In addition, the guidance should be clear that there is no requirement to include results from exploratory biomarker tests in the study report.
IV. Submission of PG Data D. Compliance with 21 CFR Part 58	Line 394	The guidance needs to address if a test is run to non-GLP standards would it be considered not valid
Section V. Format and Content of a VGDS	Lines 410 – 470	The guidance should clearly indicate there is no requirement to file additional VGDS data with the Agency. This could cause an unnecessary burden on sponsors.
V. Format and Content of a	Line 432	AZ recommends that there should be more clarity on what FDA will or will not do with the data in the VGDS. Is the submission of data in

Section	Page or Line Number	Comment or proposed replacement text
VGDS		a VGDS covered in the informed consent? AZ recommends that the format of VGDS be as flexible as possible, to encourage companies to participate.
V. Format and Content of a VGDS	Line 461	<p>Replace existing text of</p> <p>Validation of SNP by SSCP (single-strand conformation polymorphism) or other assays</p> <p>with:</p> <p>Validation of SNP by gold-standard techniques such as direct sequencing</p>
V. Format and Content of a VGDS	Line 462	Genotyping data produced for publication does not normally include raw data since SNP data is by its nature binary and can often be adequately summarized by means, standard deviations, etc. In addition many protocols and informed consents state that data will be presented only as a group (aggregate) in order to protect patient confidentiality. AZ recommends that the format of VGDS data be extremely flexible and the inclusion of raw genotyping data is not a requirement.
VII. FDA Review of PG Data	Line 499-509	AZ recommends that there be further guarantees/safeguards around use of VGDS data within the same company and/or from other companies. Further clarification is necessary in the guidance to elucidate this point.
VII. FDA Review of PG Data	Lines 498 – 509	The guidance should include the provision for the sponsor to arrange meetings with FDA on the VGDS and that there should be fixed timeframes for scheduling and conducting the meetings (potentially a Type B category).
VII. FDA Review of PG Data	Line 500	Further clarification is necessary regarding the role of the IPRG, who will be involved in the IPRG and how will they be selected? If the members are ‘experts’ in pharmacogenetics there is the potential they are more likely to have vested interests in the field (including business interests) posing risks to the confidentiality of the data. The Intellectual Property (IP) position should also be clarified, e.g. does a full report, abbreviated report or VGDS count as a publication for IP purposes?
VII. FDA Review of PG Data	Line 506	The process by which PG data across different drugs in a given class will be evaluated should be transparent and flexible. This process should address the following questions: How are trends observed by IPRG to be communicated? What is included in the term “significance”? How will the FDA notify sponsors? If sponsors and the FDA disagree on the significance of VGDS findings, how is this to be resolved?

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VII. FDA Review of PG Data	Line 539-540	The implication from this sentence is that the FDA will approve a drug for which safety data is available only on a population predicated on a pharmacogenetic test. AZ recommends confirmation that this is the intention of the guidance.
Glossary	Line 596	AZ recommends a list of known valid biomarkers. This should include separate validated alleles and the scientific rationale for each. In addition, there should be the opportunity for this list to be extended and for the agreements to be made during development on what criteria would need to be met.
Glossary	Line 605	AZ recommends a flow diagram of what is needed to turn a probable valid biomarker into a known valid biomarker. The flow diagram should contain the criteria/scientific thresholds for moving from exploratory to probable valid biomarker status?
Appendix B	Line 713	On page 20, point 3 under submission of PG data to a new NDA the document talks about probable valid biomarkers and in the schedule on page 19 it is said that “if meets point 2 or 3” it should be “abbreviated report to NDA/BLA”. Contrasts with table on p26, ‘Probable Valid Biomarker The FDA recommends submission, using algorithm in section IV.B. of the guidance’. Clarify whether required or recommended.
Appendix D	Line 748	If the sponsor declares that PG data is “voluntary”, does FDA have to agree or not? What if there is a different opinion from different sponsors regarding the same biomarker on what is a valid biomarker and what is not? We recommend a clear and transparent process on who determines the biomarker status.
Appendix D	Line 773	If a probable valid biomarker changes status to known valid biomarker post the VGDS process, what are the regulatory implications of this change? The definition of VGDS/exploratory research PG/probable valid biomarker data and the implication of a potential change over time should be discussed in the guidelines.
Appendix D	Line 808	A known valid biomarker may be used in very different context – is it then a known valid biomarker or exploratory? E.g. MHC markers are well known in the transplantation field, and are tested in highly regulated laboratories for this purpose. If these same markers were used in exploratory research on response to a drug, AZ would recommend that the data could be submitted as a VGDS, since its clinical significance in this context is not known.
Appendix D	Line 820	If a company develops a pharmacogenomic diagnostic test (for safety or efficacy) can another company with a drug in the same class be required to use it? AZ recommends that, unless the test affects safety, this should be the sponsor’s decision. This should be stated clearly in the document.

Section	Page or Line Number	Comment or proposed replacement text
Appendix D	Line 844	If a synopsis is submitted, can the FDA require more data? AZ recommends that it should be the sponsor's choice to submit a brief synopsis to report exploratory research, rather than a detailed report containing raw data.