

Date: MAY 09 2006

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

Re: Docket Number 2006D-0012
Response to FDA Call for Comments
Draft Guidance for Industry and Food and Drug Administration Staff;
Pharmacogenetic Tests and Genetic Tests for Heritable Markers

Dear Sir or Madam:

Reference is made to the February 9 2006 Federal Register notice announcing the request for comments on the Draft Guidance for Industry and Food and Drug Administration Staff; Pharmacogenetic Tests and Genetic Tests for Heritable Markers.

AstraZeneca has reviewed this draft guidance, and our comments are attached.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 Brian Abbott, Associate Director, at (302)886-1437

Sincerely,



Barry Sickels, Executive Director
Regulatory Affairs
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BS/bma

Enclosure

2006D-0012

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**AstraZeneca comments on the Draft Guidance for FDA and Industry Staff:
Pharmacogenetics Tests and Genetic Tests for Heritable Markers**

General Comments

We welcome this initiative from the FDA to clarify the requirements for the development and regulation of pharmacogenomic and genetic diagnostic devices. We particularly welcome the emphasis on the 'least burdensome approach' and believe that this will facilitate progress in the field. The flexibility and high level of the guidance is appreciated.

- **Comment 1**

The scope of the guidance is described in the Introduction (p4) as concerning the development and regulation of pharmacogenomic and genetic diagnostic devices. We recommend that the word 'device' is included in the title to avoid confusion with tests that are carried out in a research or exploratory context.

- **Comment 2**

We note that somatic mutations are not covered by the guidance. In the future we would welcome a similar guidance that included somatic mutations.

- **Comment 3**

We welcome the distinction between pharmacogenetics and genetic tests, which we believe will be helpful.

- **Comment 4**

The inclusion of an additional appendix with examples of submissions of pharmacogenetic and genetic test devices would be helpful.

Specific Comments		
Section	Page or Line Number	Comment or proposed replacement text
I.	p1	The phrase 'array based' is used several times in the document. Since this phrase is generally used to refer to RNA microarray technology, we recommend the term 'DNA array based'.
III. A.	p3	The intended use of the device refers to the 'marker' the device is intended to measure. We recommend that the word 'genotype' is used in this context rather than 'marker'.

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Section	Page or Line Number	Comment or proposed replacement text
III. A.	p4, 1 st bullet	The use of the term 'enrichment' should be clarified since a potential use of pharmacogenetic tests is to select patients for inclusion in clinical trials, which is, by definition, enrichment. It should be made clear that this is a statistical issue that can be addressed by careful study design (e.g. determination of marker frequency and clinical prevalence in the intended use population).
III. A.	p4, 2 nd bullet	The words 'many samples' should be clarified since the same considerations apply if few samples (from a large population) are tested.
III. C.	p6, item 1	We welcome the flexibility on the potential use of a variety of sample sources as technical controls. This is particularly important for assay development for tests involving rare alleles.
III. C.	p6, item 2	<p>The section on input sample quality should be clarified:</p> <p style="padding-left: 40px;">If you do not intend to provide sample preparation reagents in your kits, you should provide specifications for assessing the quality of the assay input sample so that users can validate their own sample preparation method and reagents.</p> <p>It is more usual for genetic testing kits to provide specifications for quantity of input DNA rather than quality, so we presume that the FDA are thinking in terms of a simple quality measure such as A260/280 ratio, is this correct?</p>
III. C.	p7-9	These pages contain several technical terms (e.g. "correct call" fraction) that are specific to DNA microarrays and are not likely to apply to other types of genotyping technology. To avoid confusion we recommend that this should be clarified.
III. C.	p6, item 9	We recommend that a description of the recommended workflow is included. This will have a direct impact on the potential for sample carryover.
III. C.	p6, item 10	This point assumes that all the alleles that are capable of being detected by the device are known. Should the submission include some disclaimer if alleles or genotypes have only been detected within certain ethnic groups and not others?

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III. E.	p11, item 2	We welcome the rigor of the comparison of novel technologies with bidirectional sequencing. However, sequencing may produce misleading results in certain circumstances, e.g. if there is a polymorphism sited in one of the priming sites, and if there is a polymorphic deletion spanning the amplicon (such as the CYP2D6*5 allele). We recommend that sponsors should be able to use other reference methods when scientifically justified.
III. F.	p12, item d	We are unclear whether the term "clinical cut-off" refers to a technical cut-off that is to be related to a clinical endpoint, e.g. peak height, or a clinical cut-off that is to be related to a technical marker, e.g. cholesterol level. Please clarify (and also on 1st paragraph, p13).
III. F.	p13, item f	We are concerned in the potential use of unpublished data to be used as supporting material for the evaluation of the clinical validity of a new test. The publication of data implies a level of rigor and peer-review that may not be present in unpublished data. If unpublished data is to be used, we recommend that it should be made clear that the sponsors should provide evidence of rigor and independent peer review.
IV.	p14, interpretations	We would welcome some further examples of appropriate wording for interpretation of results (e.g. in a further appendix).
Appendix 1	p16, item 1	We would welcome some clarification on the extent of diversity of ethnic groups that should be included in study design, e.g. should these be the major ethnic groups in the US, and should they all be equally represented in terms of sample size (item 5)?
Appendix 1	p1, item 10	We welcome the expectation that new diagnostic devices should ideally be validated in a prospective clinical trial and that associations should be replicated in an independent dataset. The paragraph implies that it may be possible to use retrospective datasets in the situation where a prospective clinical trial is not possible and statistical procedures have been carefully evaluated. We recommend that this potential use of retrospective datasets should be clarified, even if they are not the preferred option.