GEN-PROBE

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July 15, 2003

Dockets Management Branch [HFA-305]
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20850

Re: Comments for the *Draft Guidance for Industry and FDA Reviewers; Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns*
[Docket No. 03D-1020]

To Whom It May Concern:

In an effort to providing industry feedback to FDA, I have solicited the comments of our Regulatory group regarding the FDA draft guidance document, *Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns*. Our comments/questions are summarized in the following matrix, which lists the elements in question, the corresponding page number, and our concerns. Please notify me when a final draft guidance is issued.

Thank you for your attention to this matter.

Sincerely,

Alan Maderazo, Ph.D.

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Draft guidance reference	Page	Comments/Questions
We recommend that the sponsor or manufacturer consult with FDA to determine the appropriate type of submission	2	• Is the use of a form 513(g) appropriate for this consultation? • Reference the appropriate meeting guidance documents for CBER and CDRH.
FDA recommends a separate application for each intended use that requires unique and separate supporting studies.	4	• Some tests could potentially be bundled if there is an appropriate justification. This recommendation should be removed. • Make reference to *Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products; Guidance for Industry and FDA*
***Assay** sensitivity: ability to accurately identify positive samples.*	5	• Sentence should read: "**Analytical** sensitivity: ability to accurately identify positive samples" since this is under the *Analytical Laboratory Studies* section.
Assay specificity and interfering substances (endogenous and exogenous).	5	• Sentence should read: "**Analytical** specificity and interfering substances (endogenous and exogenous)." since this is under the *Analytical Laboratory Studies* section
"Clinical truth": Define clinical truth as it will be used in evaluating the clinical performance of the device.	7	• Clarify how to address this for genetic tests that have an undefined endpoint. In some cases presence or absence may be a sufficient end point and the document should permit this. • Should also clarify that determination of "clinical truth" should be discussed with FDA prior to clinical trials (e.g. pre-IDE protocol submission).
For diagnosis, relative sensitivity and specificity and discrepant resolution can be very misleading and are not appropriate for primary evaluation of approvability. FDA recommends reporting of positive and negative percent agreement.	11	• Appears that FDA is trying to change the paradigm for performance claims. However, the lab industry expects sensitivity/specificity performance claims; they don't use positive and negative agreement. This change in the FDA review process is not appropriate in this guidance.
Recently, statistical methods have been developed that allow comparison of methods with the unknown true value being measured.	12	• Provide a reference for these statistical methods.
A Bland-Altman scatter plot of the difference between paired measurements from the two methods versus their average is especially useful for detecting trends in systemic and random errors over the measurement range.	12	• Provide a reference for this statistical method. • Is this an FDA preference or an established statistical method? Clarify this is a consideration and not required.
Throughout this page, the phrase *control method* is used	12	• ***control** method* should be replaced by ***reference** method*