Amersham

To:	Docket Management Branch (HFA-305)
Re:	Docket Number 03D-0120 *Draft Guidance for Industry and FDA Reviewers; Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns*
Contact Person:	Daniel Mannix, Ph.D., Vice President Regulatory Affairs (609) 514-6494
Date:	July 17, 2003

General Comments

Amersham shares the opinion expressed in the *Federal Register* notice that multiplex tests including microarrays will have a number of clinical uses. Thus, this draft guideline is a timely document to begin the process of introducing the Agency's opinions concerning the regulatory requirements for these products. We await the issuance of the next draft guideline and look forward to further FDA, health professional and industry dialogue.

We recommend that the next version of this guideline be partitioned into sections for DNA and RNA tests and further separated into 510(k) versus PMA products. While the FDA may have limited experience with product approvals at this time, reliance on the definitions for and general requirements of non-significant and significant risk devices should allow FDA to delineate the type of information and data needed to support a notification versus an approval process.

Additionally, section numbers are repeated within the document, which is somewhat confusing. Consider renumbering the entire document.

We believe it would be helpful to include, at the end of the document, a list of other relevant CDRH guidelines and references to other sources of related information.

Specific Comments

Section I, Purpose

Page 2 contains a statement that sponsors should consult with the FDA to determine the appropriate type of submission (PMA versus 510(k)). We suggest that all such meetings should involve division directors to ensure that regulatory requirements are consistent across all products and that the least burdensome approach is always applied.

On page 2, paragraph 3 contains recommendation to file protocols as pre-IDEs. We recognize FDA's initiative to provide guidance at early development stages. However, in order for this process to serve all parties: industry, FDA and the health community, FDA must ensure resources are available for this process and a specified timeframe for responding to such protocols should be included in the next version of the guideline. Additionally, we recommend

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Section I, Purpose (Continued)

adding a section to cover the manner in which disagreements are to be handled. Or, alternatively, consider issuing a separate guideline for a protocol review process.

On page 2, the third paragraph, we suggest that the third sentence read "or" instead of "and". "Depending on claims...submissions are expected to be processed as PMAs, de novo 510(k)s or traditional 510(k)s.

Section III, Genetics versus Expression

The second paragraph on page 3 ends with the statement: "Clinical studies should account for disease prevalence in the populations studied." We believe that this statement is too restrictive because it emphasizes the use of genetic tests for determining disease status. However, other genetic tests (e.g., those for ADME related genes) categorize patients according to their ability to metabolize drugs and are not disease related. We suggest the following alternative language: "Clinical studies should account for prevalence of the correlated phenotype in the populations studied."

Section I, Intended Use of a Test or Device

This section recommends a separate application for each intended use that requires unique and separate supporting studies. We believe the FDA should specifically state in the guideline that sponsors are allowed (within the same type of filing i.e., 510(k) or PMA) to cross-reference an already approved application for data that is common to one or more applications. Furthermore, until the FDA has gained experience with these types of products, we suggest that the FDA put in place a mechanism for overall review to ensure consistency across all review divisions.

Section II, Analytical Validation

Page 4, section A, paragraph 2 lists elements of arrays and multiplex platforms that should be well characterized. We completely support FDA's position that microarray design, components, and processes should be well-characterized. We agree that design and process validation along with the proper quality gates must support a well-characterized product because decisions about disease state and/or treatment may be made based on the results of such tests. We urge the FDA in the next draft of the guideline, to further define those aspects that FDA considers critical for a well-characterized product including guidelines for finished-product characterization and quality control.

On page 5, section C.2, there is a recommendation to describe the potential for sample carryover. We request that this phrase be clarified. Is this recommendation based on failure modes effect

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Section II, Analytical Validation (Continued)

analysis (FMEA) where a risk priority number is given or is it based on a quantitative measurement, such as a probability calculation?

Section III, Comparison Studies

On page 6 for items A through E, it appears that item C is a subset of item A and that item D is a subset of item B. It may be useful to revise this section and, as noted earlier, to separate requirements for PMA versus 510(k) products. With such an approach, the FDA may be able to provide more specific guidance on this important topic.

Section IV. B. Clinical Validation

In item B.2, the FDA leaves to the sponsor the definition of "clinical truth". In many cases the sponsor can give this definition; however, the definition is anticipated to be very different for a product in the 510(k) process compared to a product in the PMA process. The statement should be clarified because we believe the FDA will impose a higher standard of proof for a PMA product.

We believe the first sentence of number 3, Clinical Data should read: "Validate phenotypic correlations with expression patterns or genotypes by ensuring the use of a statistically adequate number of specimens to validate each intended use."

The fourth line of this section states: "...verify with a second detection system, if applicable." We are concerned over the interpretation of this statement and believe the guideline should specify the proposed criteria for applicability and whether or not a second detection system is required for all samples or for a selected subset. This statement goes beyond the usual FDA requirement of comparing a device with a predicate device or reference method.

Section V

It should be noted that the text for Section V missing.

Appendix I, Number 8

Item 8 states that the intended use of the product should be supported with data that are representative of the population and to include a diversity of ethnic groups. It is not the marker or mutation that may vary according to ethnicity, but rather the frequency of its allelic forms. Therefore, we recommend the following statement: "Include a diversity of ethnic groups if the frequency of the marker/mutation alleles varies according to ethnicity."

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Appendix I, Number 9

It seems reasonable to predict that for any test method, there will be false negative and false positive results unless a test is developed that has perfect sensitivity and specificity. False positive and false negative results will be encountered in clinical testing and will have to be addressed as noted in section III, Comparison Studies. It is unlikely that false positive and/or false negative samples will be available as standards. Until such standards are available, we believe Number 9 should be deleted.

It should be noted that the text for numbers 10-12 is missing.

Appendix II

While this section intends to impart some guidance on the statistical tests to be used, we find the section too general. We believe the FDA should review the statistical environment that is specific for array data and use that information to develop specific advice for this Appendix. Alternatively, the appendix can be deleted and Section IV. B. 5 can be modified to include a statement that analyses techniques must be clearly described and defined and be generally accepted by the scientific and medical community.

The third paragraph and following bullet points note the limitation of comparison testing without a measure of truth [clinical truth?]. Again, consideration should be given to separating requirements for 510(k) devices and PMA devices as this approach might allow FDA to impart better or more specific guidance.

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