ABBOTT LABORATORIES

Corporate Regulatory and Quality Science

April Veoukas
Corporate Regulatory Affairs
D-3QC, AP6C-1
E-mail: april.veoukas@abbott.com

100 Abbott Park Road
Abbott Park, Illinois 60064-6091
Facsimile: (847) 938-3106
Telephone: (847) 937-8197

July 17, 2003

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

RE: *Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers [Docket 03D-0120]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns," published in the Federal Register on April 21, 2003 at 68 FR 19549.

Thank you for the opportunity to provide these comments. We are pleased with the level of insight and detail that went into this first draft of the guidance document. Additionally, we are pleased with FDA's plans to issue a second draft document after review of comments and revision of the document. Regulation of multiplex tests involves many issues, and we agree stakeholders will benefit from this two-tiered approach.

To further the dialogue with stakeholders we recommend FDA provide its responses to the comments received on the first draft with its issuance of the second draft. It is especially important to understand FDA's rationale for not accepting submitted comments to avoid re-submission of the same comments upon issuance of the second draft.

It would also benefit FDA stakeholders, if CDRH reiterated the scope of this guidance document is limited to the preparation of PMA and 510(k) applications for multiplex assays intended for commercial distribution, and that it is not intended to provide guidance on the use of mircroarray assays in drug discovery and development. A document intended to provide guidance on both topics would be extremely complex, and unduly delay the guidance the diagnostic industry seeks regarding multiplex assays.

03D-0120

C10

ABBOTT LABORATORIES

GENERAL COMMENTS

As this document is intended to provide guidance on a wide variety of multiplex technologies, striking the appropriate balance as dictated by assay technology is essential. Multiplex assays consist of a wide variety of methodologies, including, DNA chips, comparative genomic hybridization, expression chips, bead-based or other solid matrix support, and homogenous real-time PCR. Each technology presents different issues of validation, safety, and effectiveness, even internal quality control will vary by methodology. For known technologies, such as DNA arrays and solid matrix support, we recommend fleshing these items out in more detail in the guidance document. Our comments below provide specific recommendations.

SPECIFIC COMMENTS

Section I. Purpose

In the purpose, FDA states "depending on claims and *information available* multiplex and array submissions are expected to be processed as PMAs, de novo 510(k)s and traditional 510(k)s" (emphasis added). Specifically, in regards to multiplex and array submissions, please clarify what type of additional information FDA will evaluate as it considers submission type. For example, does FDA plan to consider the multiplex testing methodology, number of sequences or independent validation of the included genes?

Section III. Genetics vs. Expression

It is recognized in this guidance document that measuring changes in expression profiles will raise different issues of validation, safety, and effectiveness relative to measuring changes in DNA. DNA changes, however, can be further sub-divided into two distinct categories each with their own issues of validation. These two categories of DNA changes are: 1) nominal (e.g., sequence changes, epigenetic changes such as alterations of DNA methylation, and chromosomal translocations; here the variants cannot be placed in sequential order and the presence or absence of each possible form is detected) and 2) ordinal (e.g., copy number changes; here the variants are sequential with respect to each other and the number of copies of a sequence is detected). Unlike nominal changes, ordinal changes lend themselves to internal validation controls because copy number changes of near-neighbor chromosomal regions are common.

To reflect these two distinct categories of DNA changes, we recommend modifying the definition of genetic test as follows:

> The measurement of expression changes, whether RNA or protein, will raise different validation and safety and effectiveness questions than the measurement of DNA changes or variations. Further, it is recognized that the measurement of nominal DNA changes will raise different validation questions than the measurement of ordinal DNA changes.
>
> "Genetic" tests: DNA differences are fixed, whether germinal or somatic. Results from these tests can generally be described as dichotomous (either

present or not present), trichotomous (homozygous A, heterozygous, homozygous B), categorized (e.g., haplotypes). Interpretation of tests designed to measure these types of differences will be, in most cases, straightforward. Nominal changes (e.g., sequence changes) will raise different validation questions than ordinal changes (e.g., copy number changes) because ordinal changes lend themselves to internal validation controls. DNA array tests ~~nevertheless~~ should be carefully designed and highly reproducible, and have well-established performance. Clinical studies should account for disease prevalences in the populations studied.

Section: Recommendations for the Preparation of the Multiplex Test Application

General:

The guidance document describes assay characteristics, which influence the types of data and statistical analyses FDA will request. Because of the wide variety of multiplex assays we recommend supplementing the examples provided in this section with the following additional information (indicated by underlined text):

(1) ***intended use*** (for example, to detect cytochrome p450 enzyme alleles or to detect chromosomal copy number changes)
(2) ***indications for use*** (for example, diagnostic or predictive or prognostic for disease, response or sensitivity)
(3) ***methodology*** (for example, polymerase chain reaction or comparative genomic hybridization)
(4) ***technical interpretation of results*** (for example, positive for variant alleles or gain or loss of chromosomal copy number).

Sub-Section II Analytical Validation:

Subpart A: Design and Manufacturing:

Under the "design and manufacturing" section, we recommend FDA address quality control as it pertains to the wide variety of multiplex devices. Specifically, that the multiplex technology will dictate the type of quality control that is adopted. Quality control and validation of non-array testing platforms will vary from that of array platforms. Clarification of this point in the guidance document is important.

The guidance document provides the types of analytical data necessary to demonstrate the device performs accurately and reliably under given conditions. We recommend the inclusion of a fourth item, "elements for self validation of the assay performance." Given the inherent complexity of certain multiplex assays, it is important to develop an internal validation process that is logical, representative of the assay characteristics, linked to the quality of the assay performance, and related to the safety and effectiveness of the device.

Subpart C: Array and Data Processing

In item three, of this section, FDA recommends firms "develop computational methods using the CDRH software development and validation guidance documents." Readers are referred to FDA's database for these documents. We recommend FDA cite the specific names of these guidance documents in this Multiplex Tests guidance document. Additionally, if there are specific sections in these software development and validation guidance documents that pertain to array and data processing, we recommend FDA identify these sections. This additional information will better able industry to prepare the studies necessary for analytical validation.

Section IV. Clinical Evaluation Studies Comparing Test Performance to Accepted Diagnostic Procedure(s)

Subpart B: Clinical Validation:

General:

We agree with FDA's decision to leave different ethnic and racial mixes out of this document, noting recent literature supports such an approach (See Wilson JF et al *Population Genetic Structure of Variable Drug Response*, 29 Nature Genetics 265 (2001) (concluding "commonly used ethnic labels are both insufficient and inaccurate representations [of genetic diversity]")).

Subpart B. 3. Clinical Data:

The use of RT-PCR as a second detection system, if applicable, is appropriate. However, we note expression may not always correlate one hundred percent with RT-PCR.

Requiring testing on a "statistically adequate number of specimens" is of concern because of the large number of patients with various combinations of multiple markers. The advantages of using multiple markers could be lost, if one is prohibited from using such markers as members of a multiplex test because of complex issues related to obtaining a statistically adequate number of samples to fully validate the test.

For certain tests, a statistically adequate number of specimens for each phenotype that the test is designed to detect would facilitate collection of the appropriate data. The clinical data for a CYP2D6 assay designed to identify poor metabolizers and extensive metabolizers, for example, would consist of a statistically adequate number of specimens of each poor metabolizers and extensive metabolizers. It would not, however, involve a statistically adequate number of specimens for each of the genotypes, *3/*3, *3/*15, etc.

With other tests, the use of alternative statistical approaches applied to existing literature or previously conducted clinical trials would enable one to collect the necessary clinical validation data. DNA specimens collected from completed clinical trials might be used for prospective clinical validation by blinding those genotyping the specimens from the clinical data and having a pre-specified analysis plan.

We encourage FDA to work with industry to design meaningful and appropriate clinical studies for multiplex assays. To further this end we recommend FDA include the

following statements in the guidance document, "FDA will consider alternative approaches to clinical validation, such as design based on phenotype, alternative statistical approaches, or previously collected specimens. Sponsors, however, are encouraged to discuss such approaches with FDA prior to conducting clinical validations to ensure the study design is appropriate for the assay and its intended use."

Subpart B. 6. Literature:

We recommend replacing "array-based test system" with "multiplex test system" to reflect the fact that literature could be used to support patterns in other types of multiplex test systems, as well as array-based test systems.

Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 938-3106. We look forward to continued dialogue with the Agency during the development of this guidance document.

Sincerely,

April Veoukas

April Veoukas, J.D.
Manager, Information & Policy
Corporate Regulatory Affairs and Quality Science
Abbott Laboratories