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Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and
Management Services
Food and Drug Administration
5630 Fishers Lane
Room 1061, (HFA-305)
Rockville, MD 20852

Pleasanton, July 18, 2003

Re: Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers [Docket No. 03D-0120, 68 Federal Register, 19549-19550, April 21, 2003]

Dear Sir or Madam,

Roche Molecular Systems welcomes the opportunity to comment on proposed Guidance on multiplex assays and arrays for heritable DNA markers, mutations and expression patterns. This proposed guidance reflects many of the areas covered in prior discussions between RMS and FDA, and represents a very useful first, formal step towards developing a clear, unburdened pathway for regulating assays utilizing this powerful new technology.

General Comments

The guidance document would be easier to follow if it was broken out into the 3 main areas where microarrays will be used, germline DNA genotyping, mixed sample genotyping (HIV, cancer), and mRNA expression analysis. Each of these applications has unique characteristics that need to be addressed. The guidance document does not deal with any of the important pre-analytical issues such as mRNA stabilization or tissue microdissection for cancer applications.

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03D-0120

Introduction

Purpose

The first sentence in the Introduction states that the purpose of the document is to provide guidance on preparing and reviewing premarket approval (PMA) submissions. Later, in the discussion of the purpose of the document, it is acknowledged that the scientific issues may also apply products requiring 510(k) notifications.

- It is suggested a reference to class I and II devices, or to 510(k) notifications be included in the first sentence of the Introduction to reinforce the fact that the Guidance is not applicable to Class III products only.

Least Burdensome Approach

The guidance describes the intention to use the Least Burdensome Approach to submission review. An example of an application of this approach would be in the selection of the regulatory pathway for the device.

The least burdensome regulatory pathway may vary by assay and intended use.

FDA should consider what path to recommend on a case-by-case basis for each application.

Points to consider when making this decision include the following:

Intended use

Predisposition

Aid to diagnosis

Prediction of risk for recurrence or disease severity

Therapy choice/dose

Safety Issues

Treatment availability

Risk from misclassification

Benefit to the patient

Genetics vs. Expression

Genetic DNA tests (vs. DNA expression assays) were described as measuring differences that are "fixed, whether germinal or somatic". Genetic tests may in fact be more diverse in their intended use.

It is suggested that a phrase be added to indicate that genetic tests may include tests for mixed cell populations, e.g., somatic mutations, HIV resistance, as well as tests for epigenetic status, e.g. methylation.

Guidance is provided as to the nature of test results, and their interpretation. In addition factors to be considered in product design are described, including disease prevalence, and factors influencing expression changes.

Important pre-analytical issues such as mRNA stabilization or tissue microdissection for cancer applications are not dealt with.

RECOMMENDATIONS FOR THE PREPARATION OF THE MULTIPLEX TEST APPLICATION

Analytical Validation

Design and Manufacturing

The need for analytical data to support internal or external controls and calibrators is described, but details of requirements for control are not provided.

The requirements for controls for multiplex or array-based tests have not been clearly defined, beyond those described in the CLIA regulations.

The respective responsibilities of the test manufacturer and the clinical laboratory in providing the appropriate controls is as yet unclear.

Test manufacturers should use a risk-based approach in the design of assay controls that is specific for the technology and the intended use.

Validation of Specific Performance Characteristics: Analytical Laboratory Studies

Assay sensitivity is defined as the ability to accurately identify positive samples. This view of sensitivity is too restrictive, and does not adequately reflect genetic test sensitivity.

Genetic tests typically detect specific changes in DNA sequence, each of which may be found at some frequency in the normal population. "Mutation" may include deletions or duplications of target sequences.

Analytical sensitivity is typically determined using samples with known quantities of a specific analyte in the clinical specimen. In the case of genetic tests, analytical sensitivity may be instead be defined as the quantity of target DNA that can be reproducibly detected by the assay system.

Clinical Data to Support Intended Use

Clinical Validation

Clinical Truth

Sponsors are asked to "define clinical truth as it will be used in evaluating the clinical performance of the device."

Defining truth in this case must deal with several possible confounding factors, including:

Greater accuracy of the array method in providing sub-type information than the current established methods

The need for a clear definition of what is expected from an independent validation

The long duration that may be required for studies to collect patient outcome data.

Clinical data:

The guidance document states that genotype/phenotype correlations should be supported by clinical data. FDA had previously suggested that "literature bridges" could be used to link analytical validity to clinical validity and clinical utility.

The use of published literature correlation studies should be an acceptable option to demonstrate genotype/phenotype relationships to FDA

Verification of the test results using a second detection system (e.g. quantitative RT-PCR), if applicable, is described.

The selection of a second detection system should be made using a least burdensome approach. Second detection systems should be similar in performance (e.g. both quantitative, both semi-quantitative, both yes/no) to the test system under evaluation.

The need to define the number of samples from the normal population, and to stratify test samples demographically is noted.

Demographic data are likely to be less important for expression assays than for genotyping assays.

In the case of genetic screening assays the normal population may also be the test population.

Reference ranges

The NCCLS document NCCLS C28 "How to Define and Determine Reference Intervals in the Clinical Laboratory", (http://www.nccls.org/) is listed as a source to be consulted when establishing reference ranges.

This document provides broad information for calculating reference intervals for quantitative analytes, and may not be appropriate for defining the normal variation in allele frequencies across populations for genotyping tests.

We appreciate the opportunity to provide comments on this important document and anticipate that these comments will prove useful to you as you finalize this guidance. Roche Molecular Systems also looks

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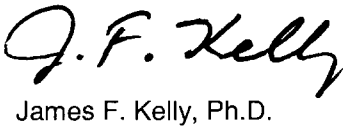
forward to working with FDA as the regulatory strategy for Multiplex/Array Tests continues to evolve.

Sincerely,



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