May 8, 2006

Division of Dockets Management
HFA-305
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: **Docket No.2006D-0012: Comments on the FDA Draft Guidance for Industry and FDA Staff - Pharmacogenetic Tests and Genetic Tests for Heritable Markers**

Dear Sir or Madam:

The following comments regarding the FDA draft guidance on Pharmacogenetic Tests and Genetic Tests for Heritable Markers represent the combined input from the drug and diagnostic arms of the Roche Group: Hoffmann-La Roche Inc, F. Hofmann-La Roche AG and Roche Molecular Systems Inc. We recognize our unique opportunity to provide integrated comments from the both the therapeutic and diagnostic industry perspectives and accordingly in the document that follows we will term this combined input as from Roche. In the text below, we provide general comments on key issues, followed by specific section by section comments and recommendations.

General Comments

This document represents a useful replacement for the February 27, 2003 draft guidance "Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers" and reflects much of FDA's recent, successful experience with the regulation of pharmacogenetic and genetic tests. However, there are several keys areas in this guidance that would present significant hurdles to test manufacturers attempting to bring to market new pharmacogenetic and genetic tests for IVD use.

There is a general concern that pharmacogenetic testing has been singled out as the topic of this guidance when the emphasis should be on drug-treatment-related biomarkers in general. Moreover, the document lacks any statement clarifying that there is no fundamental difference between a genetic test and other tests.

A major concern is that several sections of the draft Guidance include language that may not be consistent with the Least Burdensome Principles applicable to the development and approval of genetic tests (or any drug-treatment related biomarker test). The emphasis on demonstrating the clinical validity of a test for a genetic marker in addition to analytical performance significantly increases the scope of the evaluation studies. In addition, data requirements for a submission are expanded to reflect prevalence of the disease or condition, geographic distribution of markers,

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predictive value. Requirements for statistically significant data to demonstrate clinical validity become particularly burdensome if they are applied to markers associated with rare diseases.
The data requirements for regulatory submissions are often broadly described and do not reflect the risk associated with the intended use. Documentation requirements related to manufacturing and testing for Premarket Approval Applications and for 510(k)s are not clearly delineated.

The concept cited in this document of using published literature to create a bridge between analytical data and clinical validity has been shown to be an effective tool when there is sufficient pre-existing scientific knowledge related to the marker. However, the requirement that the published studies focus on the same study population and utilize a test method of the same technology of the device would greatly reduce the availability of this option.

A third concern is that the document, while attempting to be comprehensive is in many aspects superficial and imposes certain standards that are not necessarily relevant for genetic or biomarker-based testing and therefore may be overly prescriptive in terms of the device design. For example, within the Guidance are performance specifications that have been commonly applied to IVD devices, including precision, cut-off, analytical specificity, carryover, sensitivity, specificity. The STARD publication is also cited as a reference for reporting diagnostic accuracy. These same concepts appeared in the draft Premarket Review Template document that CDRH created as part their involvement in the Secretary's Advisory Committee on Genetic Testing. It may be useful to include concepts for assay evaluation that are specific to genetic tests. An example being those described by the CDC-sponsored ACCE project.
(http://www.cdc.gov/genomics/gtesting/ACCE.htm#References).

Specific Comments

Section III A. Intended Use of a Device

In paragraph 2 of this section, manufacturers are encouraged to file separate applications for each intended use that has unique and separate supporting studies.

> *Comment:* Depending on its expected use in a laboratory setting, a single device may be designed and configured to target more than one marker. In this case the product could not be marketed without clearance or approval of any of the target markers. In addition, such a device may have a single package insert, and software configured to only report results for multiple markers. The requirement for filing separate applications for such a device would create unnecessary redundancies and further complicate the review process.
>
> **Recommendation: Separate applications should not be required for a device that is specifically designed to target multiple markers.**

The third paragraph and subsequent bullet points are intended to highlight issues associated with tests meant to detect rare events.

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In the first bullet point of this section, it is stated that for low prevalence alleles, genotypes, and mutations sufficient patients should be tested to provide a significant number of positive results.

> *Comment:* The need to demonstrate identification of rare genotypes, including rare homozygotes, in prospective studies is not a least burdensome approach. In addition, this statement is inconsistent with the position in Section C.1: "When fresh samples for rare alleles, genotypes, or mutations are scarce, we will consider the use of archived or retrospective samples. Although natural samples are preferred, we will also consider artificially prepared materials, such as plasmid DNA or amplified gene segments."
>
> **Recommendation: There is no need for large prospective studies. Detection of rare genotypes can be effectively demonstrated by testing banked natural samples, clones and synthetic samples. The effectiveness of these approaches obviates the need to perform large prospective studies involving low prevalence genetic markers.**

In the second bullet point of this section it is stated that the ethnic makeup of the study population should be based on the frequency of the alleles, genotypes, or mutations.

> *Comment:* Individual determinations of ethnic identity can be problematical, including those based on self-reporting. If banked samples are used to determine genotype detection rates knowledge of national origin or ethnicity can create additional issues in procuring such samples
>
> **Recommendation: The frequency of a genetic marker in various populations can be described based on published literature. Stratification of test specimens by ethnicity of national origin should not be a requirement of the performance studies**

The third and fourth bullet points highlight difficulties concerning test performance when evaluating rare events.

> *Comment*: These statements do not fully address the various scenarios under which the particular cited issues (need for enrichment or high false positive rate) may or may not be acceptable within a given study. This may depend upon the purpose of the study in evaluating the analytical or clinical performance characteristics of a pharmacogenetic test. Moreover, these few bullets are not exhaustive enough to provide a useful list of issues that need to be considered when designing studies for the evaluation of tests intended to detect rare events.
>
> **Recommendation: Consider rewording this portion of the "intended use" section (paragraph 3 and associated bullets) to convey a high-level message regarding difficulties of testing for rare events. Reference could also be made to literature or other sources where a comprehensive treatment of the topic has been made.**

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In the fifth bullet point of this section it is stated that to demonstrate the validity of predictive screening tests, and to evaluate penetrance of a marker, it may be necessary to perform long-term follow up studies.

> *Comment:* Long-term, longitudinal studies may be useful to support test reimbursement, but should be beyond the scope of the initial regulatory application.
>
> **Recommendation: Long-term, longitudinal studies, when needed, should be performed**

Section III B. Device Design

In this section the requirements for Device Descriptions are described and associated regulations pertaining to 510(k) applications (807.92(a)(4)) and for Premarket Approval Applications (814.20(b)(3)(ii), 814.20(b)(4)) are cited. Specific references are made of the need for description of the methods used for attaching probe material to a solid surface and for functional testing to address the potential for probe cross-contamination during manufacturing, irrespective of application type.

> *Comment:* The need to provide details of manufacturing methods and in process and QC testing are beyond the scope of 510(k) applications. The August 12, 2005 CDRH guidance "Format for Traditional and Abbreviated 510(k)s" recommends that manufacturers include a brief description of the device design that may include diagrams, dimensions, tolerances, and/or schematics.
>
> **Recommendation: The requirements for Device Design and Device Descriptions for 510(k) applications and for Premarket Approval Application should be treated separately, since the former do not require detailed descriptions of manufacturing procedures and test methods.**

C. Analytical Studies

This section describes the requirements for analytical studies to support specifications for sample preparation and quality, precision, controls and calibrators, cut-off, interference and crossreactivity, assay conditions, carry over and cross-hybridization. Regulations describing performance data requirements for 510(k) applications (21 CFR 807.92(b)) and PMAs (21CFR814.20(b)(3)(v) are cited.

In Part 1 of this section, General analytical performance considerations, manufacturers are asked to test samples in the analytical studies that span the recommended input concentrations.

> *Comment:* The requirement would greatly expand the scope of such studies, and is not a least burdensome approach.
>
> **Recommendation: Requirements for input concentration should be established in dedicated studies, and need not be demonstrated in multiple analytical studies.**

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In Part 2 of this section, "Sample characterization and specifications" validation requirements for specimen processing methods and specimen handling and storage are described. It is stated that the sponsor should demonstrate that the chosen sample preparation method consistently

Recommendation: It would be useful to include in this section a description of methods that may be employed to expand the types of specimens that may be tested (e.g., blood, buccal cells, saliva), including the use of bridging studies, that would allow manufacturers to avoid repeating all performance studies with each specimen type.

In Part 4 of this section "Precision (Repeatability/Reproducibility)", it is stated the test panel for precision studies should include samples that span the recommended input concentrations.

Comment: Depending on the required diversity in the reproducibility test panel, the addition of multiple input concentrations would add unnecessary complexity to these studies.

Recommendation: The reproducibility test panel should include specimens near the analytical sensitivity of the assay.

This section also includes a statement that tests should be performed at different times of the day.

Comment: The benefit of performing precision testing at different times of the day is unclear. For nucleic acid-based tests, for example, it is unclear what variability is being addressed by this approach.

Recommendation: On board stability studies are more effective for determining reproducibility of test results within the recommended daily testing periods. The recommendation on "different times of day" should be omitted

Part 5 "Controls and calibrators", includes a statement that the level of controls should span the recommended sample input concentrations.

Comment: The need to include kit controls at multiple input concentrations is not a least burdensome approach.

Recommendation: The need for controls should be risk based mitigations associated with risk assessments, and on customer requirements. Single level system controls should be sufficient for qualitative tests.

In the Part 7, "Analytical specificity (interference and cross-reactivity studies)", it is noted that potential inhibitory substances may not be removed during specimen preparation and may also interfere with specimen preparation itself. It is recommended that studies be performed to examine the effect of potential interfering substances on sample preparation and assay performance.

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Comment: The need to test for interfering substances in patient specimens should be based in part on the demonstrated efficiency of the specimen preparation method.

Recommendation: If a highly efficient specimen preparation method is provided as part of the test system, studies of possible interfering substance should not be required.

Section III D. Software and Instrumentation.

In Part 2 of this section "Validation of instrumentation" it is recommended that instrument descriptions and test data be provided for value assignment, feature location, size, concentration, volume, drying of small samples, effect of small volume reactions and its impact on test results. In addition, instrument calibration and procedures and potential instrument sources of uncertainty are recommended to be described.

Comments:
Details regarding the design and performance of a 510(k)-cleared IVD instrument need not be provided in a reagent submission.

Standard laboratory equipment used for sample preparation (spectrophotometer for absorbance measurement, fluorometer for DNA quantification or gel analysis of amplifiable DNA) should not need separate validation.

Recommendation: If a previously 510(k)-cleared instrument is included in the test system instrument design and performance information need not be repeated in the reagent submission. Standard laboratory equipment should be validated as part of the test system.

F. Clinical Evaluation Studies Comparing Device Performance to Accepted Diagnostic Procedure(s)

This section contains detailed descriptions for the design and content of clinical studies to support the safety and effectiveness of a pharmacogenetic or genetic test.

Comments: The need for clinical studies should be dictated by the device type, intended use, design, safety profile, and clinical knowledge of the genetic marker. Alternatives to clinical studies should be FDA will always consider alternatives to clinical studies when the proposed alternatives are supported by an adequate scientific rationale. Our recommendations for clinical testing typically depend on many factors including device type, intended use, design, safety profile, and clinical experience.

Recommendation: Alternatives to clinical studies for genetic tests should be considered that have an intended use of genotype identification and in cases when the clinical importance of the genetic marker is well understood. These alternatives may include analytical data, including comparisons to sequencing data, and the use of published

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literature to demonstrate clinical validity. The performance of the test in a user setting can be validated in external reproducibility studies.

In Part (a) of this section the need to define "clinical truth" in clinical evaluation studies is described.

Comment: The need to determine the clinical status should be based on the intended use of the test.

Recommendation: Genotype identity may be determined by sequencing methods. Tests that are not intended for diagnostic purposes should not be required to have determinations of clinical status for patients from whom test specimens are obtained.

In Part (b) it is recommended that, if necessary genotype/phenotype correlations be validated.

Comment: The need to determine genotype/phenotype correlations should be determined based on current knowledge of the penetrance of the genetic marker .

Recommendation: In cases where genotype/phenotype correlations are well-understood, additional studies to demonstrate penetrance should not be required.

In the bullet points in Part (b) requirements for statistically determined performance data from studies of demographically stratified normal populations are described. The need for demographic stratifications of performance data for each disease, condition, or genotype is also described.

Comment: The requirements for testing specimens from a normal population, and for demographic stratification of test results, should be dictated on the intended use and indications for use of the test. The need for statistically determined numbers of specimens from multiple categories of patients does not representative a least burdensome approach for test validation.

Recommendation: This requirement should not pertain to tests for which the target population for a test is narrowly defined or for when demographic information is not required for genotype determinations.

In Part (f) of this section it is stated that literature used to support bridging from analytical to clinical performance should involve studies of similar patient populations and tests of the same technology.

Comment: The relevance of published data for determining the link between analytical and clinical performance is dictated more by efficiencies of the two methods in genotype determination, irrespective of the technologies used. Testing a patient population similar to that described in the literature may be cumbersome.

Recommendation: Data from published studies, utilizing a test of different technology with similar genotype coverage, should be usable to support the clinical performance of

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a new test, providing that the analytical performance (genotype detection) of the two methods are comparable.

G. Clinical Effectiveness of the Device

In the first paragraph of this section it is recommended that clinical data be submitted for both PMAs and *de novo* submissions.

Comment: The need to include clinical studies in *de novo* applications should be dictated by the intended use of the test and the pre-existing knowledge of the clinical usefulness of the test result.

Recommendation: *De novo* applications for genetic tests with an intended use of genotype identification should not require clinical studies to demonstrate safety and effectiveness. Accuracy of genotype detection can be determined in studies utilizing clinical specimens, where results from sequencing are compared to those obtained with the genetic test. The performance of the test in a user setting can be validated in external reproducibility studies as part of the de novo application.

In Part 2 of this section, "Established Markers", it is stated that comparability should be established between the new test and the test used in the literature bridging studies

Comment: The relevance of published data for determining the link between analytical and clinical performance is dictated more by efficiencies of the two methods in genotype determination, irrespective of the technologies used.

Recommendation: Data from published studies, utilizing a test of different technology, should be usable to support the clinical performance of a new test, providing that the analytical performance (genotype detection) of the two methods is comparable.

Section IV. Labeling

The "Directions for Use" paragraph includes a statement referring to how the pharmacogenetic/genetic test is to be used on patients.

Comment: This reference does not apply to IVD devices since they are not used directly on patients, but rather for *in vitro* examination of patient specimens.

Recommendation: Rephrase this statement to narrow the scope to *in vitro* use.

In the "Stability" section it is recommended that stability data be provided to support the reagent shelf life.

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Comment: The FDA Guidance document "Format for Traditional and Abbreviated 510(k)s August 12, 2005" states that "For a submission that identifies a shelf life for the device, your shelf life should be supported by appropriate bench tests and/or sterilization (packaging) validation," and does not suggest that stability data be provided in the application. The need to include stability data in a 510(k) application represents a burdensome requirement and is not in keeping with current FDA guidances.

Recommendation: The requirement for the submission of stability data in a 510(k) application for pharmacogenetic and genetic tests should be deleted.

The "Performance" section includes a statement that failed assays (no calls) should be treated the same as disagreements (miscalls) in the performance data.

Comment: The risk associated with incorrect results is distinctly different from cases when no results are reportable.

Recommendation: No call results should be reported separately from incorrect results.

Appendix I: General considerations for planning and evaluating clinical studies

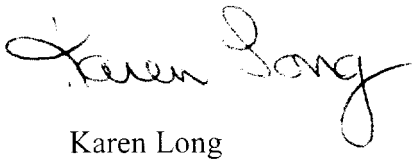
In Part 7 of the appendix it is stated that samples from individuals with diseases or conditions that may cause false positive or false negative results should be tested, if appropriate.

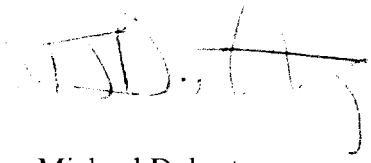
Comment: Because of their specificity for human DNA or RNA targets, the likelihood of false results being associated with patient clinical status is far less likely for genetic tests than for clinical chemistry tests and tests for microbial pathogens.

Recommendation: Unless indicated by risk assessment, the regulatory submissions for genetic tests should not be required to assess the impact of disease condition on test accuracy.

Roche is pleased for the opportunity to provide these comments. We hope that FDA will finds these points useful in finalizing this document and we look forward to working with FDA and industry to further discuss the issues identified above.

Respectfully submitted,





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