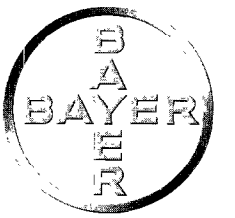
Bayer HealthCare
Diagnostics Division



July 16, 2003

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

Re: Docket No. 03D-0120; Industry Comments

Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns; Draft Guidance for Industry and FDA Reviewers

This letter is to provide Bayer Diagnostic's comments to the above-referenced Draft Guidance. Bayer appreciates the opportunity to provide comments in an effort to continue the dialogue with stakeholders regarding the basic framework for the types of data that should be included in a multiplex submission. We acknowledge and appreciate that this is the beginning of an iterative process to develop guidance that is in the best interest of science and patient safety. Bayer looks forward to further participation in this process.

Bayer comments on this Draft Guidance are as follows:

1. Bayer would like clarification of FDA's definition of multiplex testing. In the Draft Guidance, multiplex tests are "tests that assay multiple analytes simultaneously". In the Federal Register, multiplex tests are "assays yielding multiple, simultaneous results". For a test to be considered a "multiplex test", would it have to assay multiple analytes and yield multiple simultaneous results? In the case of expression testing, for example, there might be a pattern consisting of multiple expressed genes that, when expressed, give a single diagnostic result. In this case, would each separate expressed gene be considered a different analyte producing a different result? Does FDA consider DNA sequencing an application of multiplex testing?

2. In a related question, Bayer would like clarification of FDA's perspective on the distinction between multiplex testing and assays with multiple intended uses. In the Draft Guidance FDA recommends, for tests with multiple intended uses, a separate premarket application for each intended use that requires unique and separate supporting studies. For a multiplex test where multiple analytes are being measured, would FDA require separate supporting studies and separate premarket applications for each analyte? This can become very burdensome from an industry perspective. For example, clinical studies to support each marker, mutation or pattern could get very complex and expensive and may not provide additional scientific value or enhance patient safety. In addition, it would be very burdensome to file and maintain multiple submissions for a single multiplex test, particularly if the analytes are regulated by different centers, for example CBER for HIV analytes and CDRH for other analytes.

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3. In an effort to reduce regulatory and industry burden, would FDA consider this a good opportunity to create an inter-agency agreement between CBER and CDRH for regulation of multiplex testing of analytes that would otherwise cross between the two centers?

4. Bayer would like clarification of FDA's reasons for including DNA markers, e.g., SNPs and mutations, in the same guidance document as expression patterns. As recognized in the Draft Guidance, DNA differences in genetic tests are fixed and interpretation will be, in most cases, straightforward. Expression patterns, on the other hand, are dependent on a variety of factors and may be difficult to interpret. It does not seem necessary to elevate DNA marker regulation to the same level as expression pattern regulation. Given the significant differences in these assays and the different validation issues likely to apply to these assays, Bayer would support guidance that very clearly delineates between these assays. Would FDA, for example, see any value in issuing separate guidance documents?

5. What would be considered an adequate reference method for the expression pattern assays? Would FDA require, for example, that each individual expressed gene in an expression pattern be compared to a separate reference method or reference sequence, or could there be a reference pattern established through clinical studies? For DNA marker and mutation assays, would DNA sequencing be an acceptable reference method or a gold standard for defining the reference genotype? The Draft Guidance states that clinical studies should account for disease prevalence in the populations studied. If an allele is found to be uncommon or rare, must it be included in the reference samples?

6. Will it be required that the manufacturer understand what transcripts are being measured (what gene products) or will the result of the measurement and the disease association be sufficient?

7. What performance characteristics (i.e., sensitivity and specificity) will be required for pharmacogenomic based tests predictive of adverse drug events or efficacy of therapy?

8. The Draft Guidance does not address validation of the probe sequences on the microarray chips. Can FDA provide clarification of how each spot on the microarray should be validated? Would it be necessary, for example, to verify the probe sequence at each spot on the array? What manufacturing controls and lot to lot quality controls will be needed to evaluate the performance of the array? What types of controls will be needed to calibrate the array and the array reading instrument by the customer? With regard to array validation, can guidelines be established that are broad enough to include all types of arrays/technologies, i.e., solid and liquid arrays?

Sincerely,

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