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August 19, 2003

Via FedEx

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry regarding Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns
Docket No. 03D-0120

Dear Sir or Madam:

Enclosed please find comments of the American Clinical Laboratory Association on the draft guidance regarding Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns.

If you have any questions or comments, please feel free to contact me.

Sincerely,

Erin Lewis Darling

ELD:del
Enclosures

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American
Clinical Laboratory
Association

Comments of the American Clinical Laboratory Association on the Draft Guidance for Industry regarding Multiplex Tests for Heritable DNA Markers, Mutations, and Expression Patterns

[Docket No. 03D-0120]

The American Clinical Laboratory Association ("ACLA") is pleased to submit these comments on the draft guidance for industry ("Draft Guidance") issued by the Center for Devices and Radiological Health on April 21, 2003 regarding multiplex tests for heritable DNA markers, mutations and expression patterns.[1] ACLA is an association representing independent clinical laboratories throughout the United States including local, regional and national laboratories. In the United States alone, clinical laboratories perform millions of tests each year for physicians and other health care professionals. ACLA members are regularly engaged in the development and performance of new types of testing to help monitor various medical conditions. Laboratories routinely perform laboratory-developed tests ("LDTs") for heritable DNA markers, mutations, and expression patterns using devices that incorporate multiplex technology. Many of these LDTs are developed using Analyte Specific Reagents ("ASRs") developed by third parties. As a result, ACLA members would be significantly affected by this Draft Guidance if it is interpreted to narrow the scope of the ASR regulations or it significantly disrupts the flow of devices that incorporate multiplex technology.

ACLA is concerned that there may be confusion about how the Draft Guidance impacts ASRs using multiplex technology. On its face, the Draft Guidance addresses only the data requirements for PMA and 510(k) submissions for devices that incorporate multiplex technology. The Draft Guidance does not purport to define the boundary between clinical assays which incorporate multiple ASRs (which are exempt from premarket approval in accordance with the ASR Rule[2]), and devices that incorporate multiplex technology and are complete "test systems" and therefore require FDA approval. Because the Draft Guidance does not address the question of this boundary, ACLA is concerned that many ASRs used in LDTs today might arguably be construed to come within the scope of this Draft Guidance. Thus, we are writing to request that the Draft Guidance be clarified to state that it is not intended to revise the ASR Rule and does not mandate FDA approval of multiplexed reagents where each of the multiplexed reagents otherwise meets the definition of a Class I ASR.

Multiplex technology, as incorporated by laboratories into laboratory-developed tests, is simply one component of many laboratory-developed assays. The multiplex technology to which the Draft Guidance is directed may be "embedded" in many different technology platforms, including such diverse platforms as sequencing instruments (which may be programmed to detect various genetic sequences); simultaneous PCR reactions; liquid-phase, bead-based probes; and micro-array chips.

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[1] See 68 Fed. Reg. 19549 (April 21, 2003).
[2] See 62 Fed. Reg. 62243 (Nov. 21, 1997).

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Multiplexed assays have two primary advantages over equivalent panels of separately-performed assays:

- Small sample volume. Because the several tests are performed on one patient sample (blood, cerebral spinal fluid, etc.), a much smaller volume of this sample needs to be drawn. This is especially important for pediatric and geriatric patients.

- Enhanced quality assurance. The clinical scientist is in a better position to evaluate the pattern of results from a multiplex test. Unusual reactions are often immediately evident and permit real-time investigation and/or confirmation testing. This enhanced quality assurance reduces risks to patient care.

In all other respects, notwithstanding the additional costs that may be incurred to run multiplex testing, including the cost of multiple reagents, the analytical testing platform(s), supplies, and so forth, a multiplexed assay is technically the same as running the component tests sequentially or in parallel.

Some examples of multiplexed tests that have been used in clinical laboratory practice for many years include the following:

- *Streptococccus pneumoniae* susceptibility. The effectiveness of childhood vaccination against the various types of *streptococcus pneunomiae* is evaluated by detection of antibodies to the various types in the serum of the vaccinated child. Using a Luminex bead-based assay, the 12 most common such types can be detected in a multiplex reaction on just .01 mL of sample. As noted above, this characteristic of a multiplexed assay is particularly important for these pediatric patients.

- Autoimmune disease panel. Another common application of multiplexed technology is in the diagnosis of autoimmune disease. Six or more of the specific autoantibodies that are associated with autoimmune disease can be screened for in one bead-based assay. This reduces the sample-volume requirement for the mostly geriatric and female population that needs this testing.

- Anti-HIV drug level monitoring. Proper dosing of HIV-positive patients is critical to the effectiveness of therapy, and depends among other factors on the patient's metabolism of the drugs. Serum drug levels of protease inhibitors or reverse transcriptase inhibitors are commonly measured simultaneously using liquid chromatography coupled with tandem mass spectrometry.

- Diagnosis of leukemia/lymphoma using flow cytometry. Leukemia and lymphoma are commonly diagnosed using multiplexed flow cytometry. In this assay, various species of cells in the patient's blood are quantitated by attaching marker molecules to unique cell surface proteins and then running them past a laser detection system.

If the FDA is proposing, through the Draft Guidance, to change the ASR regulations to exclude this type of multiplex technology from Class I under the ASR regulations, ACLA believes that such action must be undertaken through the formal rulemaking process.

ACLA recommends that the Draft Guidance be clarified to explicitly state that it does not mandate FDA approval of multiplexed reagents used in laboratory-developed tests where each of the multiplexed reagents otherwise meets the definition of an ASR. ACLA appreciates the opportunity to submit these comments. If we can be of any further assistance, please feel free to contact us.

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