

Coalition for 21st Century Medicine Overview of New FDA Guidance Documents

INTRODUCTION

[The Coalition for 21st Century Medicine](#)¹ is a group of emerging diagnostics companies along with other relevant concerned stakeholders that have joined together with the goal of applying the latest in scientific advances – including applications of knowledge from the Human Genome project – to the creation of innovative molecular tests and services. The promise of these advanced applications has greatly improved healthcare delivery and reduced overall healthcare costs with some early successful examples².

As you may know, the US Food and Drug Administration (FDA) has recently released two new draft guidance documents that could potentially have the affect of significantly reducing access to important molecular tests for clinicians and the patients they serve. Therefore, the Coalition is working collaboratively with the FDA to implement an appropriate regulatory approach that ensures safety and quality. In addition, there is legislation that was introduced in the US Senate by Senator Barrack Obama (D-IL) and draft legislation being circulated by Senator Edward Kennedy (D-MA) touching on this same area of regulation.

We are contacting critical healthcare constituents that that may be impacted by reduced access to innovative molecular tests with comprehensive background information surrounding this guidance. Specifically, we would like to ask for your support in a very important way. For your convenience, here is a synopsis of:

- Apparent FDA concerns that resulted in the release of the guidance documents
- Concerns from review of the issues with these recently published documents
- Proposed solution to address FDA concerns and industry issues

THE COMMENT PERIOD ON THESE GUIDANCE DOCUMENTS CLOSSES ON MARCH 5, 2007. AFTER REVIEWING THE INFORMATION, WE WOULD LIKE TO REQUEST THAT YOU SUBMIT COMMENTS AS SOON AS POSSIBLE TO THE FDA:

DIVISION OF DOCKETS MANAGEMENT
HFA-305
FOOD AND DRUG ADMINISTRATION
5630 FISHERS LANE
ROOM 1061
ROCKVILLE, MD 20850
RE: **2006D-0336** (FOR ASR GUIDANCE) AND **2006D-0347** (FOR IVD/MIA GUIDANCE)

PLEASE ALSO SEND A COPY OF YOUR COMMENTS TO THE OFFICE OF YOUR LEGISLATORS. THE COALITION WOULD ALSO APPRECIATE A COPY:

ATTN: DAVE BARNHARDT
The Coalition for 21st Century Medicine c/o DEWEY SQUARE GROUP
1001 G STREET NW, SUITE 500
WASHINGTON, DC 20001

FDA CONCERNS

The FDA has not specifically stated the public health concerns it has with Laboratory Developed Tests³ (LDTs) or Analyte-Specific Reagents (ASRs), nor has the Agency explained the way that the regulatory approach proposed in the draft guidances would address these undisclosed concerns. The FDA appears to be focusing on genetic tests, particularly those involving multiple variables –including DNA, RNA, protein or other clinical variables – that are combined using simple or complex mathematical algorithms to provide a score or index. In the Draft Guidance Documents, the FDA describes such tests as "In Vitro Diagnostic Multivariate Index Assays" (IVDMIAs). The FDA is concerned that physicians may not be able to understand the score or index result in a simple, intuitive way as they might understand other single clinical or diagnostic variables. This has resulted in a draft

¹ Description attached (*separate document*)

² Some examples are attached (*separate document*)

³ LDT's are validated by CLIA certified laboratory using and/or other reagents purchased by or prepared by the laboratory.

guidance document published by FDA that would define such tests as a "medical device" and now subject to full FDA regulation.

The FDA believes that many LDTs offered by CLIA laboratories are analytically validated, but not clinically validated meeting the Agency's standards for an FDA-cleared or approved IVD test kit⁴. Further, the Agency appears to be concerned by a perceived lack of consistency associated with genetic testing between laboratories. At the same time, the Centers for Medicare & Medicaid Services (CMS), responsible for running the CLIA program, withdrew from plans to establish a Genetic Subspecialty under CLIA, despite this request being on its regulatory rulemaking docket from the CDC and others for over 7 years.

In September 2006, the FDA's Office of In vitro Diagnostics (OIVD) published two Draft Guidance Documents⁵ for public comment.

Issues with the Draft Guidance Documents

While we are in agreement that some level of additional regulatory oversight makes sense to ensure quality testing, there are several critical issues that need to be addressed:

- The Guidance Documents represent a significant change in the FDA position in both the ASR and LDT areas, and may possibly interfere with the practice of medicine
- Both documents are ambiguous, creating profound negative effects immediately and in the future – by stifling innovation of new technologies, delaying or freezing the development of many tests currently in production and ultimately decreasing access for patients to important tests and services
- The FDA should follow a formal notice and rule making process to ensure complete, on-the-record input from all affected individuals and organizations

There are many, far-reaching consequences should these documents be implemented as currently written – affecting physicians, patients, pathologists, laboratories and diagnostic companies across many diseases. To assist you in submitting comments that are the most relevant to the impact on disease diagnosis and care management, two documents are attached that provides a comprehensive evaluation in these areas⁶.

Proposed Solution

Based on the serious concerns identified above with the Draft Guidance Documents, we propose a solution that should satisfy FDA concerns without impacting access to critical tests and services. Clearly, there is no simple solution to these issues and any solution will require further clarification and refinement. That being said, an important start to addressing FDA concerns would be to establish a CLIA laboratory-validated test registry.

This registry could include information on analytical performance characteristics of each test, clinical data in the form of publications, laboratory experience, adverse events and other relevant informational items to ensure transparency. This would provide FDA and other regulatory bodies an opportunity to assess risk and benefit of established LDTs so that an appropriate regulatory structure based on risk can be developed instead of the somewhat arbitrary guidelines described in the Draft Guidance Documents and physicians would be aware of the performance characteristics of these tests.

Further, the legislation introduced in the last Congress by Senator Obama and the draft legislation circulated by Senator Kennedy includes some reasonable approaches toward appropriate regulation in this area. However, neither of these bills in their current form fully addresses the potential issues or goes far enough in providing appropriate incentives for the necessary development of innovative tests needed to personalize medicine and improve the diagnosis, treatment and management of complex disease.

These are just some of the ideas that the Coalition for 21st Century Medicine would like to offer on how best to approach the creation of a 21st century regulatory framework that will serve both clinicians and patients.

⁴ IVD - In Vitro Diagnostic Device

⁵ The IVD MIA guidance can be found at <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf> and the ASR guidance can be found at <http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>

⁶ "ASR Substantive FDA Filing Toolkit" and the "IVDMIA Substantive FDA Filing Toolkit"