



**FDA/CDRH Public Meeting: Oversight of
Laboratory Developed Tests (LDTs)
July 19-20, 2010**

Summary of issues and meeting notes prepared by M. Sue Leffell and Andrea Zachary, who attended the FDA LDT public meeting on behalf of ASHI.

FDA Authority: 1976 Medical Device Amendments

The 1976 Amendments provide authority for the FDA to regulate “medical devices” used for *in vitro* diagnosis. While it is not clear where the FDA’s authority lies with respect to LDTs, i.e., if this authority is not more appropriately covered under CLIA as enforced by CMS, the FDA held this public meeting assuming that it has authority over LDTs.

FDA has not, to date, exercised the enforcement of applicable regulations with respect to LDTs as a class of *in vitro* diagnostics. This includes tests developed and validated in a single laboratory and tests from FDA cleared/approved kits that are modified by a laboratory.

Reasons for FDA interest in increased oversight:

- § Tests not reviewed by FDA may be used to assess high risk and or common diseases; tests not properly validated put patients at risk of missed or wrong diagnoses
- § Even when FDA cleared/approved tests are available, labs may continue to use their own LDTs
- § Lack of “level playing field” (i.e., labs do not have to go through the FDA clearance/approval process for LDTs) creates a disincentive for manufacturers; FDA action was, in part, prompted by a petition from manufacturers
- § Concern over genetic tests/ personalized medicine

FDA’s approach: risk-based oversight of LDTs

Forum: Two day meeting for public input. Sessions:

- § Patient and clinical considerations
- § Clinical laboratory challenges
- § Direct to consumer testing
- § Education and outreach

Clinical Laboratory Session

Participants:

Professional Societies -

- Am Clinical Laboratory Association
- Association for Molecular Pathology
- Am Association for Clinical Chemistry
- Am Society for Microbiology
- Am Society for Clinical Laboratory Science
- Am Society for Histocompatibility & Immunogenetics
- Am Society for Clinical Pathology

Am College of Medical Genetics
College of American Pathologists
Clinical Cytometry Society
Society for Inherited Metabolic Disorders

Industry -

Quest Diagnostics
Becton Dickinson & Co
XdX - AlloMap
Crescendo Bioscience
Genentech
Several small biotech companies and consulting companies

Andrea Zachary presented on behalf of ASHI. Key points included:

- § Nature of histocompatibility and immunogenetic testing is largely dependent upon LDTs as there are few FDA approved tests, no approved DNA sequencers or sequencing kits, and no flow cytometers cleared for crossmatch tests.
- § Clinical Histocompatibility and Immunogenetics is a rapidly evolving field and test results require expert interpretation
- § High complexity testing for histocompatibility is regulated under CLIA. ASHI accreditation, deemed by CMS, requires extensive documentation of test validation, external proficiency, personnel competence. Personnel requirements for histocompatibility are more stringent for the technical supervisor than for other clinical laboratory disciplines, save Cytogenetics.
- § There are no FDA approved crossmatch tests; further, crossmatch would be impossible to clear or approve, since there are no standard reagents.
- § Elimination of LDTs that are not FDA cleared would stop transplantation in the U.S.
- § ASHI proposes that FDA accept or “deem” ASHI accreditation for histocompatibility tests, as well as similar accrediting agencies for other specialty tests

Societies with similar issues, concerns and suggestions as ASHI:

ACLA, AACC, ASM, Clinical Cytometry, AM College Med Genetics, to some extent- CAP

CAP's proposal: partnership between CMS, FDA, and 3rd party accreditors; supports risk based test stratification (proposal is on CAP website, CAP.org)

low risk - lab would validate & implement

moderate risk - lab validates with accreditation review

high risk - lab validates, but FDA reviews before implementation

ASCPs statement - endorsed by the Joint Commission:

support for risk based regulation with FDA and CLIA as regulating agencies

LDTs of moderate complexity/risk should be regulated under CLIA

Enhanced accreditation process through combination of government and non-gov agencies

Common issues, proposals and other suggestions:

- § High Complexity tests are already subject to validation requirements under CLIA
- § Best route for FDA, given the scope of clinical labs using LDTs, would be to partner with existing certification agencies
- § Extensive FDA approval would limit LDTs to large commercial labs.
- § Currently there are few available FDA cleared reagents and certain instruments (e.g. sequencers; Flow cytometers only cleared for phenotyping, not crossmatches)
- § Lack of appropriate validation standards and reference materials
- § Cost restraints are already severe for clinical labs

Other issues:

- § Comment from AACC - current FDA clearance/approval approach would need to be faster, more expedient for LDTs. FDA could authorize LDTs via EUA (emergency use authorization)
- § CLIA only covers analytical validation; some oversight of the correlation of test results with clinical outcomes is needed
- § Manufacturers desire a 'level playing field" but they are only subject to FDA. Labs would be subject to both CLIA and FDA approval for LDTs.

Best guess as to next steps:

Assuming the FDA decides to proceed, hopefully there will be a rule issued that will be subject to the usual period of public comment. After which the FDA will need to address those comments before issuance of any final rule. This process could take anywhere from one - four years, more likely 2-3.

Worst case scenario would be if the FDA decides it already has sufficient authority under the 1976 Amendments and simply decides how oversight of LDTs will be enforced.