

Regulatory Environment for the Approval of Diagnostic Tests

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Outline of presentation

- * Basis for FDA Oversight of In Vitro Diagnostics
- * Classification of IVDs
- * IDE, 510(k) and PMA
- * Clinical Laboratory Improvement Amendments (CLIA)
- * CLIA Classification of IVDs
- * FDA versus CLIA oversight
- * FDA Oversight of Genetic Tests
- * Government Oversight of IVDs
- * HHS Oversight of Genetic Testing Report

Federal Oversight of In Vitro Diagnostics

- * IVDs are medical devices as defined in section 210(h) of the Federal Food, Drug, and Cosmetic Act
- * Center for Devices and Radiological Health (CDRH) is responsible for oversight of IVDs at FDA
- * IVDs are subject to premarket and postmarket controls
- * IVDs are also subject to the Clinical Laboratory Improvement Amendments (CLIA '88) of 1988

In Vitro Diagnostic Products

- * IVDs are reagents, instruments, and systems intended for use:
 - in diagnosis of disease or other conditions, including the determination of the state of health, in order to cure, mitigate or treat, or prevent disease
 - and are intended for use in the collection, preparation, and examination of specimens taken from the human body
 - 21 CFR 809, In Vitro Diagnostic Products for Human Use

Classification of Devices

- * FDA classifies IVD products into Class I, II, or III
 - Classification according to the level of regulatory control necessary to assure safety and effectiveness
 - Classification determines premarket process
 - This classification in place since 1976 – prior to 1976 devices were regulated as drugs

Classification of Devices

* Class I

- Subject to the least regulatory control
- Subject to general controls
- Subject to 510(k) premarket notification

* Class II

- Subject to special controls, which could include special labeling or performance standards

* Class III

- General and special controls not sufficient to device is safe and effective for its intended use
- Premarket approval required

Classification of Devices

- * Three statutory mechanisms cover devices before marketing and sale:
 - Investigational Device Exemption (IDE), 21 CFR 812
 - Premarket Notification, 510(k), 21 CFR 807, Subpart E
 - Premarket Approval Application (PMA), 21 CFR 814

Investigational Device Exemption

- * Applies to all clinical investigations of devices to determine safety and effectiveness
- * For non-significant risk devices, investigations are considered to have approved IDE applications
 - Studies still subject to IRB approval, IC, monitoring, record keeping, etc.
- * For studies using significant risk devices, the sponsor must submit an IDE application for approval
- * Investigational use of diagnostic devices can be exempt of this regulation by waiver and if the testing:
 - is noninvasive, sampling does not present significant risk, or if results have confirmation by another product or procedure

Premarket Notification (PMN) or 510(k)

- * Evidence that a medical device is as safe and as effective or substantially equivalent to a legally marketed device (predicate device) that was or is currently on the U.S. market
- * Application submitted 90 days prior to marketing
- * Most commonly used mechanism to bring medical devices to market

Premarket Approval Application (PMA)

- * Application to request approval to market a Class III medical device
- * Also used to assess clinical data
- * For IVD products, the safety of the device relates to the impact of the device's performance, and in particular on the impact of false negative and false positive results, on patient health
- * FDA reviews PMA submissions on a 180-day timeline

CLIA

- * Act passed in 1988, in which quality standards for laboratory testing were defined
 - Proposed rule received 60,000 comments
- * Oversight by the Centers for Medicare and Medicaid Services (CMS)
- * CMS regulates laboratories that use laboratory-developed tests (LDTs) as well as FDA-approved tests
- * Laboratory can use LDT to provide testing to the public, but they cannot sell its LDTs for use by other labs

CLIA – Laboratory Certification

- * Certification by CMS or an approved accreditation body
 - Established standards for quality assurance, record maintenance, proficiency, personnel qualifications and responsibilities, and quality control
 - CMS/CLIA oversees approximately 190,000 laboratories
- * Requirements for certification depend upon the complexity of the tests performed
 - More complex tests have more stringent requirements
- * FDA responsible for categorizing the complexity for commercially marketed tests

CLIA Categorization of Tests

* Waived Tests

- Simple and accurate with little likelihood of erroneous results or no harm to patient if performed incorrectly
- All tests approved for home use

* Tests of Moderate or High Complexity

- Tests graded for complexity from 1 to 3 for each of 7 criteria (1 being lowest complexity)
- Score of ≤ 12 points; moderate complexity
- Score of > 12 points; high complexity

CLIA Categorization of Tests

* Criteria for Categorization

- Scientific and technical knowledge required
- Training and experience required
- Reagents and materials preparation
- Characteristics of operational steps
- Calibration, quality control, and proficiency testing materials
- Test system troubleshooting and equipment maintenance
- Interpretation and judgment

FDA Versus CLIA Oversight

- * FDA has stated that LDTs are medical devices and thus subject to FDA jurisdiction
- * The FDA has generally exercised enforcement discretion over standard LDTs
- * FDA's review is to ensure medical devices are safe and effective
- * CLIA's review is based upon complexity of testing to ensure accuracy

FDA Oversight of Genetic Tests

- * FDA issued final guidance in 2007 on analyte specific reagents (ASRs)
 - www.fda.gov/cdrh/oivd/guidance/1590.pdf
 - ASRs include antibodies, receptor proteins, nucleic acid sequences, etc, used to identify or quantify substances in biological specimens
 - ASRs, individually, are exempt from pre-market notification
 - However, when combined or with specific performance claims, is now viewed as an IVD
 - Genetic tests utilizing ASRs are not considered exempt from premarket notification

FDA Oversight of Genetic Tests

- * FDA issued guidance on pharmacogenetic tests and genetic tests for inheritable markers
 - <http://www.fda.gov/cdrh/oivd/guidance/1549.pdf>
 - Recommends the type of data and regulatory issues to be addressed for approval of these tests
 - Submission type depends upon the claims requested for the device; at least a 510(k), possibly a PMA
 - Provides information on device design, analytical studies, software and instrumentation, comparison studies, clinical study designs, and assessment of effectiveness

FDA Oversight of Genetic Tests

- ✦ FDA issued guidance on IVD Multivariate Index Assays (IVDMIAAs)
 - <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>
 - This IVD combines the values of multiple variables to yield a 'score' or 'index' used for diagnosis or treatment
 - The result is not-transparent or cannot be independently verified by the end user
 - IVDMIAAs raise issues of safety and effectiveness, as they will guide medical decision making
 - Even if offered as LDTs, IVDMIAAs must meet pre- and post-market device requirements

Other Relevant IVD Guidances

- * IVD Device Studies, FAQ

- <http://www.fda.gov/cdrh/oivd/guidance/1587.pdf>

- Excellent resource for FDA contacts, applicable regulations, exempt vs. non-exempt IDE studies, data, definitions, study responsibilities and other guidances

- * Statistical Guidance on Reporting IVD Study Results

- <http://www.fda.gov/cdrh/osb/guidance/1620.pdf>

- * CDRH website for Office of IVD Evaluation and Safety

- <http://www.fda.gov/cdrh/oivd/regulatory-overview.html>

Government Oversight

- * Genomics and Personalized Medicine Act (S.976)
 - <http://www.govtrack.us/congress/billtext.xpd?bill=s110-976>
 - Develop a decision matrix for review of genetic tests, plus DTC tests
 - Establish a national biobank database
 - Mandate a CLIA specialty in genetic testing
- * The Laboratory Test Improvement Act (S.736)
 - <http://www.govtrack.us/congress/bill.xpd?bill=s110-736>
 - Explicit authority for FDA to regulate LDTs
 - Require DTC tests be reviewed by FDA
 - AE reporting by laboratories using LDTs

Government Oversight

* Newborn Screening Saves Lives Act of 2007

- <http://www.govtrack.us/congress/bill.xpd?bill=s110-1858>
- Awards grants to entities to provide education and training in newborn screening of congenital, genetic, and metabolic disorders to health care professionals and laboratory personnel
- Recipients must implement guidelines and recommendations of the Advisory Committee on Heritable Disorders in Newborns and Children (HHS)
- Bill has passed the Senate and now in the House
- This bill has been introduced in the last four terms of Congress

HHS Report on Oversight of Genetic Testing

- * Secretary's Advisory Committee on Genetics Health, and Society (SACGHS)
 - Draft report (Nov 07) no longer available on line (but available from Office of Biotechnology Activities at NIH)
 - SACGHS received comments Nov 5 - Dec 21, 2007
- * Very comprehensive report and represents an excellent resource for of all aspects relating to genetic/genomic testing

SACGHS Report

* Summary

- Advances in genetic testing present challenges to the existing framework for regulation and oversight
- Central to the goal of personalized health care is the accuracy, clinical validity and clinical utility of genetic tests (<http://www.dhhs.gov/myhealthcare/goals/index.html#Goal3>)
 - Analytical validity: a test's ability to measure the genotype of interest accurately and reliably
 - Clinical validity: The test's ability to detect or predict the associated disorder or phenotype
 - Clinical utility: The net balance of risks and benefits associated with using a test in routine practice

HHS Secretary's Charge To SACGHS

- * The committee was charged to 'undertake the development of a comprehensive map of steps needed for evidence development and oversight of genetic and genomic tests'
 - Consider existing pathways that examine analytic validity, clinical validity and clinical utility
 - Is there evidence of harm associated with these attributes?
 - Roles and responsibilities of involved agencies
 - Oversight of genetic versus other laboratory tests
 - Need for proficiency testing
 - New approaches for demonstrating clinical utility
 - Value of revisions/enhancements to government oversight

Comments Received on SACGHS Draft Report

* 64 comments received on draft report

* Recurring themes in comments:

- Genetic tests are not different from other laboratory tests for oversight purposes
- Need to improve enforcement of current regulations
- Enhanced oversight of genetic testing is required
- Proficiency testing is needed
- Concerns about direct to consumer genetic tests

SACGHS Meeting

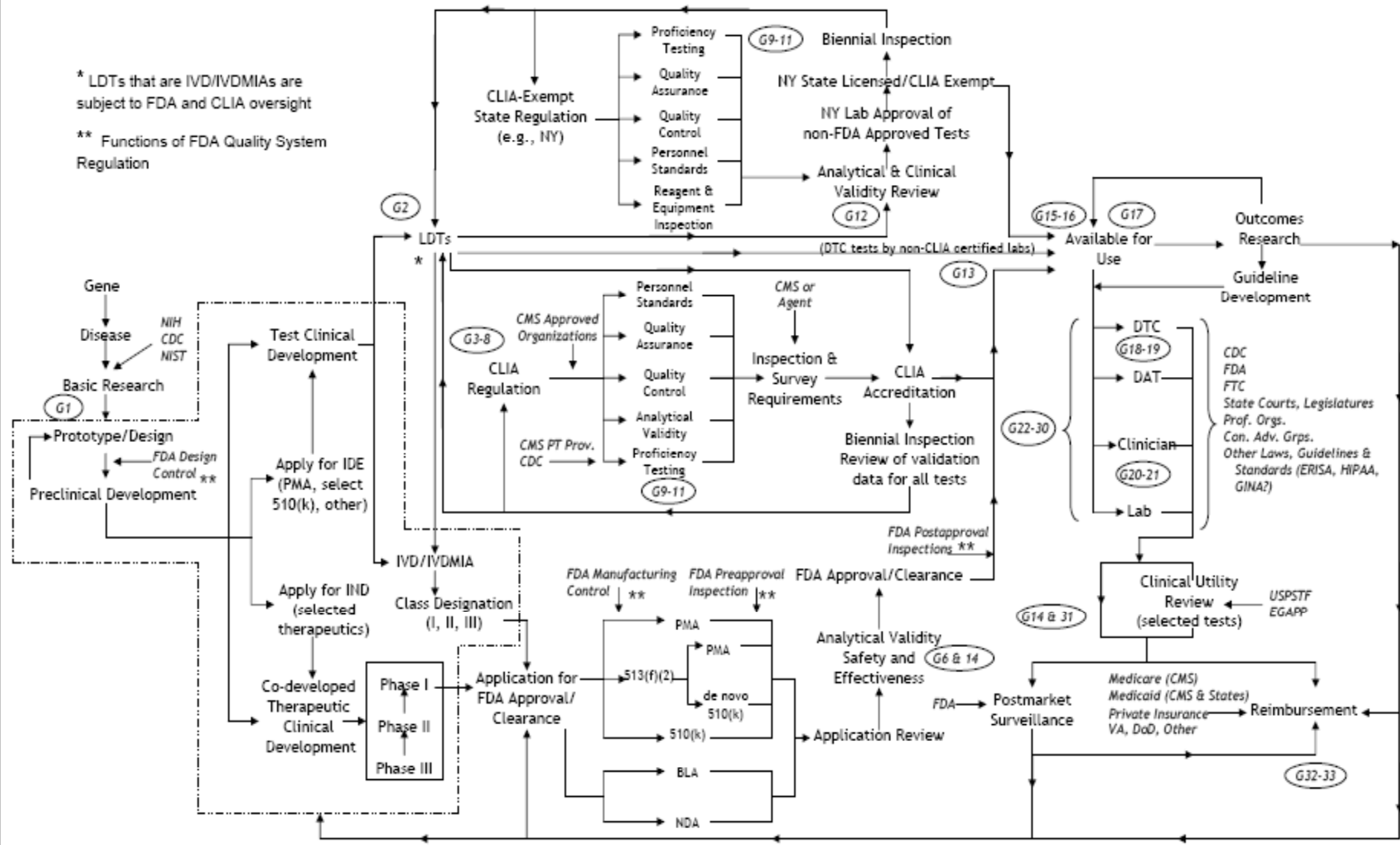
- * Meeting held in February 08 to review comments received
- * Slide presentations and transcripts available (<http://www4.od.nih.gov/oba/sacghs/meetings/2008Feb/SACGHSFeb2008meeting.htm>)
- * Final report scheduled to be submitted April 30
- * A map of the current oversight of genetic testing was constructed

Genetic Testing Oversight Map

Genetic Testing Oversight Map

* LDTs that are IVD/IVDMIA are subject to FDA and CLIA oversight

** Functions of FDA Quality System Regulation

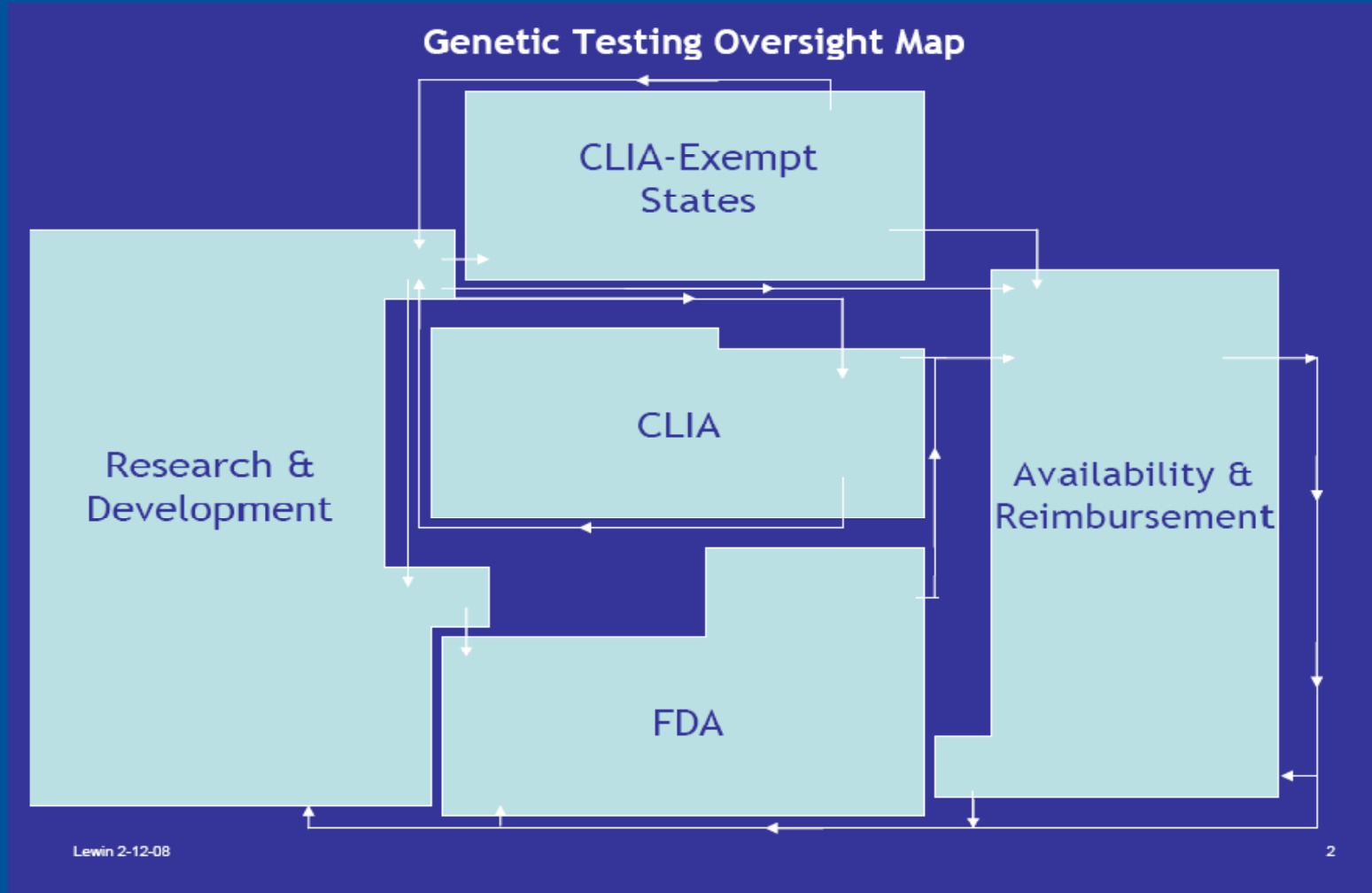


Lewin 2-12-08

Federal Courts

April 2008

Genetic Testing Oversight Map



In conclusion

- * SACGHS concludes there are significant gaps in oversight that can lead to harm
- * Regulatory oversight of genetic testing likely to increase
- * The evolution of regulatory oversight of drugs may provide insight:
 - correctly labeled, must be safe, must be efficacious
- * Clearly, genetic and genomic testing will continue to evolve rapidly and support systems (regulatory, training, interpretation of results, communication, etc) must evolve as well