The Shifting Regulatory Sands for Clinical Laboratories:

The FDA and Other Things

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Disclosures

- Ronald Weiss
  - Member, Board of Managers, AvanSci Bio, LLC
    - Early stage medical device manufacturer
  - Founding Member, Management Advisor, Decipher GenX
    - Early stage molecular diagnostics company
- Elaine Lyon
  - Member, Clinical Advisory Board, Canon U.S. Life Sciences
    - Early stage medical device manufacturer
  - Member, Diagnostic Advisory, Novartis
    - Early stage medical device manufacturer
  - Member, Advisory Board, Planning Committee, Complete Genomics
    - Translational research and clinical development

Objectives

- Consider a new proposal for Human Subjects Research protections from the DHHS
- Consider the FDA's proposed approach to RUO reagents and companion diagnostics
- Consider the proposed changes to the current regulatory framework for laboratory developed tests
- Consider the proposal to allow patients to access their test results directly from laboratories

Department of Health and Human Services

- "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators."
  - Ensure risk based protections
  - Streamline IRB review of multisite studies
  - Improve consent forms and the consent process.
  - Strengthen data protection to minimize information risks
  - Data collection to enhance system oversight
  - Harmonize safety reporting guidance across all federal agencies
  - Extension of federal regulations
  - Clarifying and harmonizing regulatory requirements

Human Subjects Research and Clinical Laboratories

- Use of de-identified residual samples not defined as Human Subjects Research for
  - Quality Control
  - Quality Improvement
  - Validation
- The lines between clinical and research testing may become thin with genome assays

Human Subjects Research Privacy Standards

- Considering adopting the HIPAA standards regarding identifiable information
- to address inconsistencies between the HIPAA Privacy Rule and the Common Rule.

Human Subjects Research Identifiable

- “Identifiable” and “de-identified” data is fluid; advances in technology and data to allow identification of an individual from data that is currently considered de-identified
- Advances in genetic and information technologies make complete de-identification of biospecimens impossible.
- DNA from a biospecimen allows data to identify individuals.
  - How realistic is this?
  - May be true for very rare variants
  - Need a comparison
- Considering categorizing all research involving biospecimens as identifiable information

Human Subjects Research
Data Security

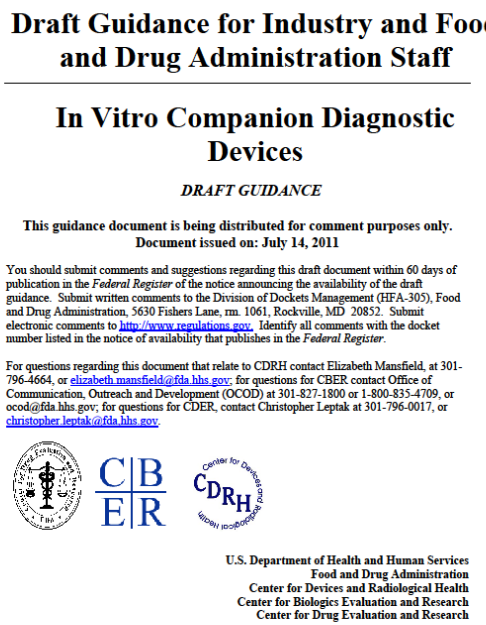
- Use data security and information protection standards
- Considering applying only to prospective collections and not retrospectively to research involving existing data.
- Data security scaled appropriately to the level of identifiability of the data.

Human Subjects Research
Cooperative Research

§46.114 Cooperative research.
Cooperative research projects are those projects covered by this policy which involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. With the approval of the department or agency head, an institution participating in a cooperative project may enter into a joint review arrangement, rely upon the review of another qualified IRB, or make similar arrangements for avoiding duplication of effort.

Companion Diagnostics

- Guidance intends to
  - Define *in vitro companion diagnostic device*
  - Explain the need for FDA oversight of IVD companion diagnostic devices
  - Contemporaneous clearance of the IVD companion diagnostic device and therapeutic product preferred.
  - Provide guidance for industry and FDA staff on possible premarket regulatory pathways and FDA's regulatory enforcement policy
  - Describe statutory and regulatory approval requirements



Draft Guidance for Industry and Food and Drug Administration Staff

In Vitro Companion Diagnostic Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.
Document issued on: July 14, 2011

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document that relate to CDRH contact Elizabeth Mansfield, at 301-796-4664, or elizabeth.mansfield@fda.hhs.gov; for questions for CBER contact Office of Communication, Outreach and Development (OCOD) at 301-827-1800 or 1-800-835-4709, or ocod@fda.hhs.gov; for questions for CDER, contact Christopher Leptak at 301-796-0017, or christopher.leptak@fda.hhs.gov.

C|B
E|R

CDRH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research

Companion DX Promise and Risk

- Development of therapeutic products that *depend on the use of a diagnostic test to meet their labeled safety and effectiveness claims*
- Identify patients
  - most likely to benefit from a particular therapeutic product
  - those not likely to respond to a therapy
  - those likely to have an adverse reaction
- Erroneous IVD companion diagnostic device results could lead to withholding appropriate therapy or to administering inappropriate therapy.

Companion DX
Excluded from Definition

- FDA does not include in this definition clinical laboratory tests intended to provide information that is useful to the physician regarding the use of a therapeutic product, but that are not a determining factor in the safe and effective use of the product.

Companion DX Labeling

- Information about the use of an IVD companion diagnostic device included in the labeling of therapeutic product
  - information about an unapproved or uncleared IVD diagnostic device may be included the labeling
- Therapeutic product labeling should identify a type of FDA approved/cleared IVD companion diagnostic device, rather than a specific manufacturer's IVD companion diagnostic device.
  - facilitate the development and use of more than one approved or cleared IVD companion diagnostic device

Companion DX

- Ideally, a therapeutic product and IVD companion diagnostic device be developed contemporaneously
- Other scenarios are anticipated
  - Product approval separately
  - IVD approval separately
- Risk-based approach to determine the regulatory pathway for IVD companion diagnostic devices

Companion DX
Other scenarios

- Approval of a Therapeutic Product
  - Already approved Therapeutic products
  - New Therapeutic Products to Treat Serious or Life-Threatening Conditions
    - no existing satisfactory treatment
    - pronounced benefits outweighs risks

- Approval of a Companion Diagnostic
  - A novel IVD device,
  - a new version of an existing device developed by a different manufacturer,
  - or an existing device that has already been approved or cleared for another purpose.

Companion DX Impact

- FDA states that most will be likely class III devices.
  - Class III devices typically need premarket approval
- Does not address Laboratory Developed Tests (LDTS)
- Impact on innovation and advancement

Companion DX Cleared Product

- FDA approved Roche/Plexxikon's Zelboraf (vemurafenib) and the companion BRAF
- Label: INDICATIONS AND USAGE
  ZELBORAF™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by **an FDA-approved test**.
  Limitation of Use: ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma.

Companion DX Concerns

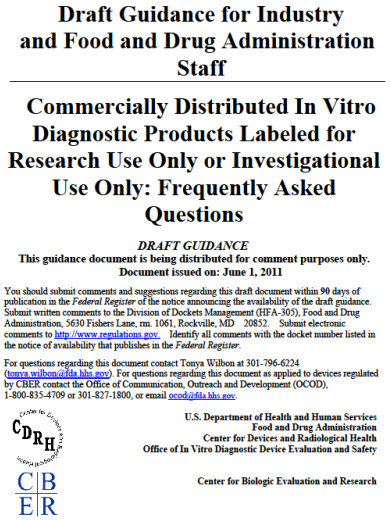
- BRAF: Label is for mutations in codon 600 (predominantly V600E) as a companion biomarker to vemurafenib, approved for use in patients with melanoma.
- Other uses of the *BRAF* V600E mutation
  - surrogate marker for *MLH1* promoter methylation in colon cancer
  - Use as therapeutic predictor in other cancers?
- Clinical significance of other mutations
  - Non V600E mutations ((V600K, V600D, and V600E2) reportedly 5 – 29%.
- Methods
  - Cobas BRAF Mutation test more sensitive than sequencing (Sanger – 20-25%)
  - Compared to pyrosequencing?

Companion DX
Feasibility for Clinical Labs

- Not feasible for laboratories to maintain multiple platforms/methods to test for the same biomarker for alternative therapeutic products
- Not practical that manufacturers will validate all possible sample types clinical laboratories may need to use for patient care
- CLIA requires clinical laboratories to validate the off label use of FDA-cleared or approved tests as if they were laboratory developed tests.
- The role of LDTs?

RUO VS LDT

- Although Laboratory Developed Tests (LDTs) are IVD products, for the purposes of this guidance document, "in vitro diagnostic product" or "IVD product" does not include LDTs.
- Frequently asked questions



Draft Guidance for Industry and Food and Drug Administration Staff

Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.
Document issued on: June 1, 2011

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document contact Tonya Wilbon at 301-796-6224 (tonya.wilbon@fda.hhs.gov). For questions regarding this document as applied to devices regulated by CBER contact the Office of Communication, Outreach and Development (OCOD), 1-800-835-4709 or 301-827-1800, or email ocod@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of In Vitro Diagnostic Device Evaluation and Safety

Center for Biologic Evaluation and Research

RUO Marketing

- **How may IVD products labeled RUO or IUO be marketed?**
  - RUO and IUO IVD products may be studied for clearance or approval,
  - May be marketed for and used in the research and investigation of other products.
  - IVD product RUO may promote and market it for research use, for example, by general discovery laboratories.
  - May promote and market it for use in a clinical investigation

RUO
Inappropriate Marketing

- **What marketing practices would FDA consider to be generally inappropriate for IVD products labeled RUO or IUO?**
  - The mere placement of an RUO or IUO label on an IVD product does not render the device exempt from clearance, approval, or other requirements, regardless of how it is marketed.
  - intended use may be shown by the circumstances surrounding the distribution of the product and the manufacturer's knowledge that its product is offered and used for a purpose for which it is neither labeled nor advertised.

RUO
Intended Use

- FDA will assess the following marketing practices as evidence of an intended use that conflicts with RUO labeling:
  - Written or verbal statements in any labeling, advertising, etc that suggest that the IVD product may be used in a clinical investigation or for any clinical diagnostic use;
  - Written or verbal statements in any labeling, advertising, or promotion of the IVD product that suggest that clinical laboratories can validate the test through their own investigational procedures and subsequently offer it for clinical diagnostic use as a laboratory developed test;
  - Sales to clinical laboratories that the manufacturer knows, or has reason to know, of use of the IVD product in clinical diagnostic in an investigation or otherwise, and support (including technical support) for those activities.

RUO
Intended Use

- **What should a manufacturer do if it learns that one of its clinical laboratory customers wants to use an IVD product labeled RUO or IUO in clinical diagnosis?**
  - Manufacturers who label their IVD products: “For Research Use Only. Not for use in diagnostic procedures,” should not sell such products to laboratories that they know use the product for clinical diagnostic use.
  - If a manufacturer learns that a laboratory to which it sells its RUO-labeled IVD product is using it in clinical diagnosis, it should halt such sales or comply with FDA requirements for IVD products.

RUO Reagents Concerns

- Tests with no FDA cleared/approved products available, or likely to be developed by manufacturers (low volumes)
- Doesn't separate test kits and test systems from general laboratory reagents.
- Will manufacturers discontinue reagents that clinical labs have validated as LDTS?
- How to encourage kit/system manufacturers to submit to FDA?
  - Need clear, consistent and flexible pathway
  - Could alternative pathways be designed?
    - Extend definition of analyte specific reagents?
      - products that are too complex to qualify as ASRs but are not full test kits or test systems?

Laboratory Developed Tests (LDT)

- Current CLIA regulatory framework
- Anticipated FDA Draft Guidance documents
- Congressional actions
- Payer responses and actions

CLIA 1988 View on LDT's

- High Complexity laboratories must establish and verify method performance characteristics before introducing a new testing procedure or method:
  - In-house developed method (LDT)
  - Modification of a manufacturer's approved method
  - Method not previously cleared by the FDA

FDA's View on LDT's

- LDT's have grown in number and are aggressively marketed to physicians and consumers
  - Many are genetics tests; some are DTC
- Clinical laboratories are acting as medical device manufacturers when they introduce an LDT
- Medical devices are the jurisdiction of the FDA
  - "Safe and effective" standard
- FDA has historically exercised "enforcement discretion"
- CLIA does not provide for oversight of "clinical validity"

The Clinical Laboratory's View

- CLIA licensed clinical laboratories provide medical services
- LDT's are not medical devices
- Clinical laboratories are not manufacturers, they are medical services providers
- CLIA should be strengthened to extend oversight of LDT's
- FDA regulatory oversight would be duplicative

FDA Proposed Guidance Documents

- In their published Guidance plans for 2012, FDA describes three new Draft Guidance documents:
  - General framework for regulatory oversight
  - Data collection from LDT providers (registry)
  - Comparing CLIA quality management systems to FDA Quality Systems Regulations for IVD manufacturers

- No details at this time

Congressional Actions

- Historical
  - The “Laboratory Test Improvement Act of 2007,” S.736, Sen. Ted Kennedy and Sen. Gordon Smith
  - The “Genomics and Personalized Medicine Act of 2007,” S. 976, Sen. Barak Obama, Sen. Richard Burr and Sen. Robert Menendex
  - The “Genomics and Personalized Medicine Act of 2010,” H.R. 5440, Rep. Patrick Kennedy
- Current Session of Congress
  - The “Modernizing Laboratory Test Standards for Patients Act” (H.R. 3207), Rep. Michael Burgess, MD (R-TX), House Energy & Commerce Committee
  - Yet to be released:
    - The “Better Evaluation and Treatment Through Essential Regulatory Reform for Patient Care Act,” Sen. Orrin Hatch (R-UT)

S. 736

- Amend FDCA to make **all** LDT's medical devices
- Comprehensive system for oversight of all LDT's
- Most LDT's classified as Class II medical devices
- All clinical laboratories using LDT's must register as manufacturers

S. 976

- Establish the Genomics and Personalized Medicine Interagency Working Group
  - Increase genetics and genomics research
  - Translate into clinical and public health improvements
  - Create a “decision matrix” to improve the oversight of genetic tests
- Similar directives in H.R. 5440

H.R. 3207, The Burgess Bill

- Would amend the Food, Drug & Cosmetic Act to exclude LDT's and DTC-genetic tests from the term "device"
- Establish a Test Registry Data Bank for LDT's, including companion diagnostics
- A laboratory notification process for all new LDT's
  - DHHS has 90 days to review for clinical validity
- Enforcement through CMS and CLIA
  - Extend oversight to direct-to-consumer genetic testing
- CMS can require additional fees to cover enforcement costs

HR 3207 and CLIA

CLIA

- Analytic validity
- Quality management rather than clinical validity
- No notification requirement
- No provision for DTC
- No LDT Registry Data Bank
- No requirement to state test capabilities
- No post-market reporting on safety
- Inspections do not address clinical validity
- 100% funded by user fees

HR 3207

- No change
- Gives CMS authority to ensure clinical validity
- Report new LDT's
- Extends oversight to DTC
- Establishes an LDT Registry
- Requires full transparency for validation using CLIA
- Investigate safety issues and report injuries/deaths
- Inspectors may request LDT clinical validity validations
- CMS can increase user fees

CAP's LDT Proposal:

"A Risk-Based Proposal for LDT Oversight"

- A public-private partnership with CAP, FDA and CMS
- 3-Tiered (risk) system
  - Based on intended-use claims
- CAP's role in establishing standardized clinical validation, documentation and inspection
- FDA to review High Risk (Level 3) LDT's

What are the implications?

- Continued uncertainty over future FDA and Congressional directions:
  - When will the Draft Guidance documents for LDT's be published and what will they say?
  - Can the "Burgess Bill" pass the House and be taken up and passed in the Senate?
    - 8 GOP co-sponsors as of December 8th
    - December 13th Coalition Meeting

Payer Responses and Actions

- Growing concerns about reimbursing for “medically appropriate” testing
  - FDA approval is one benchmark for “appropriateness”
- Rapid escalation in payments by Medicare
- Variable payer view on reimbursing for LDT’s, especially in molecular medicine
  - The infamous “code stack” and lack of transparency
- Growing interest in “laboratory benefits management” services and companies

Example: Palmetto GBA
(www.palmettogba.com)

- Medicare contractor for MAC J1 (California, Nevada and Hawaii) and MAC J11 (N Carolina, S Carolina, VA, WVA) jurisdictions
- December 2010: announced intent to deny coverage if not explicitly covered by an LCD, NCD or by CMS
  - Analytical validity, clinical validity and clinical utility
    - "Well-designed and controlled, peer-reviewed studies of clinical utility"
    - Physicians change treatment behavior based on results
- Draft LCD's published October 3, 2011
- New program announced November 2: "MolDx" to meet CMS requirements

Palmetto “MolDx” Program

- MolDx tests will be registered with “McKesson Z Codes”
  - McKesson Diagnostics Exchange Registry Module
- November 14: labs begin applying for Z Codes
  - Technology Assessment process for all new MolDx tests
    - Requires well-documented dossiers
    - Expert Panel review (academia, industry)
    - Palmetto Medical Director approval (90 days)
    - LCD for the test then issued
    - Denials can be re-submitted after 180 days
  - Existing covered tests will be require a Z Code without dossier
- Beginning March 5 all new covered tests and existing covered tests have to have a Z Code on the claim
- Process will also affect payment rate determinations and review

Industry Concerns

- MolDX was developed by Palmetto and McKesson with little or no lab input
- A local contractor code set violates Federal law
- Labs must enter into a one-sided licensing agreement with McKesson
- McKesson requests information that is either proprietary or is unnecessary for assigning a code
  - Commercial interest?
- No appeal rights for code denials
- Vague process (not transparent) for establishing the Technical (expert) Assessment Panel
- Vague clinical utility documentation requirements
- Status of existing tests, rather than new ones
- ***A very fluid process right now!***

Implications

- Burdensome compliance process
  - Duplicates what the AMA Molecular Pathology coding initiative does?
- Limit access to medically beneficial tests
- Establish precedence for other MAC's
- Carry-over to private insurance coverage policies
  - Role of the McKesson database to advise other payers and/or develop commercial products?

Patient Access to Lab Results

- "CLIA Program and HIPAA Privacy Rule; Patients' Access to Test Reports" (September 14, 2011)
  - Permit laboratories, upon a patient's request, to provide access to competed test reports
    - Further engages patients in their own care
  - Pre-empts any State laws to the contrary
  - Does not prescribe the request process (relies upon the HIPAA authorization process)
    - Failure to authenticate excepts labs from compliance

Possible Concerns & Implications

- If a patient requests that others access their reports
- If a State has a “more stringent” state law on compliance
- Effective date may be too soon (240 days after publication in the Federal Register)
  - Many labs may lack current infrastructure to comply
- “30 days from request” may not be enough for some lab tests
- How to deal with complex and sensitive test information (e.g., genetic tests)

Other Issues on the Horizon

- The new AMA Molecular Pathology CPT codes
  - Which fee schedule? When?
- The proposed AMA “multi-analyte assays with algorithmic analysis” (MAAA)
  - Formerly known as IVDMIAs
  - Implications for reimbursement and use?

Summary

- Protections for Human Subject Research bring in the question of identifiability
- LDTs will be affected by
  - FDA guidance on Companion DX
  - FDA's enforcement of RUOs
  - FDA direct regulation of LDTs
- Be active with professional societies in addressing issues
- Make your position known to your Congressional representatives

Acknowledgements

We appreciate ongoing discussions with the following organizations:

- ACLA
- AMP
  - Professional Relations Committee
  - CHAMP discussion
- ARUP
- CAP
- FDA

Questions?