FDA Regulation of Digital Pathology and LDTs

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Topics

• FDA regulation of digital pathology
• FDA regulation of laboratory-developed tests (LDTs)
• The debate over LDTs
• Next steps for the LDT draft guidances
FDA Regulation of Digital Pathology

- Digital pathology products can be regulated in multiple ways
- Depending on intended use, can be unregulated research use only (RUO), require a premarket notification submission (510(k)) or a premarket approval (PMA)
- FDA has taken the position that digital Whole Slide Imaging (WSI) systems will not be class I exempt
- FDA has cleared several digital WSI systems for limited uses such as examination of immunohistochemistry (IHC) staining reactions
- FDA has not cleared or approved digital WSI for routine surgical pathology diagnosis to replace surgical pathology using conventional light microscopy
- Regulatory challenges to broad claims
FDA Clearances of Digital Pathology in 2014

• Leica Biosystems Imaging, Inc.; July 2014: Aperio ePathology eIHC IVD System Intended use/Indications for use:
  – an automated digital slide creation, management, viewing and analysis system. It is intended for in vitro diagnostic use as an aid to the pathologist in the display, detection, counting and classification of tissues and cells of clinical interest based on particular color, intensity, size, pattern and shape.
  – The IHC HER2 Image Analysis application is intended for use as an accessory to the Dako HercepTest™ to aid in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in formalin-fixed, paraffin-embedded neoplastic tissue. When used with the Dako HercepTest™, it is indicated for use as an aid in the assessment of breast cancer patients for whom HERCEPTIN® (Trastuzumab) treatment is being considered.
  – The IHC ER Image Analysis application is intended for use as an aid to the pathologist in the detection and quantitative measurement of ER (Estrogen Receptor) or PR (Progesterone Receptor) in formalin-fixed paraffin-embedded neoplastic tissue. It is indicated for use as an aid in the management, prognosis, and prediction of therapy outcomes of breast cancer....
FDA Clearances of Digital Pathology in 2014 (cont’d)

• Omnyx, LLC; April 2014; Manual Read of the Digital HER2 Application on the Omnyx IDP System; Intended use/Indications for Use:
  – intended for use as an aid for pathology professionals in creating, receiving, managing, storing, annotating and viewing digital whole slide images from formalin-fixed paraffin embedded tissue sections stained with the Dako HercepTest. The Omnyx Manual Read of the Digital HER2 Application on the Omnyx IDP System is intended for use as an aid to the pathologist in the detection and semi-quantitative measurement of HER2/neu (c-erbB-2) in digital images of formalin-fixed paraffin embedded breast cancer tissue immunohistochemically stained with the Dako HercepTest and viewed on a computer monitor....
Additional FDA Clearances of Digital Pathology in 2013

- Ventana: November 2013; Virtuoso System for IHC ER (SP1)
- Ventana: September 2013; Virtuoso System for IHC PR (1E2)
- Ventana: September 2013; Virtuoso System for IHC PR (1E2) with Benchmark Ultra Stainer
- Ventana: September 2013; Virtuoso System for IHC Ki-67 (30-9)
- Philips: September 2013; HER2/neu IHC Digital Manual Read
- Clearances share common feature: narrow claims
- Currently customers may use for use outside of clearance (“off-label”); companies cannot promote off-label use
LDT Background

• A Laboratory Developed Test (LDT) developed and performed in a single laboratory
  – Many issues arise over collaboration
  – Not always easy to determine if an LDT

• Includes genetic tests, tests for rare conditions, and companion diagnostics

• Thousands available

• Many are standard of care
Clinical Laboratory Improvement Amendment

- Federal statute enacted in 1988 under which clinical laboratories are regulated
- Comprehensive regulatory scheme for the federal oversight and certification of clinical laboratory testing procedures and methodologies
- Requirements for laboratory personnel from pathologists and geneticists to technicians, and the documentation of procedures for individual clinical laboratory tests
- Enforcement responsibility rests with Centers for Medicare & Medicaid Services (CMS)
FDA First Asserts Authority over LDTs in 1992

• August 3, 1992 draft Compliance Policy Guide entitled "Commercialization of Unapproved In Vitro Diagnostic Devices Labeled for Research and Investigation."

• Asserts that "laboratories have been manufacturing” LDTs “either from products already on the market, or from components, and utilizing these unapproved products for diagnostic purposes.”

• LDTs are to be regulated "as any unapproved medical device."
1992 HPM Citizen Petition

• I submitted a citizen petition on Oct. 22, 1992 requesting that FDA not regulate LDTs as medical devices. I argued that:
  – FDA regulation of LDTs was inconsistent with CLIA
  – FDA lacks statutory authority to regulate LDTs
  – FDA regulation of LDTs would undermine healthcare
  – FDA can only implement such a policy through notice-and-comment rulemaking
1997 ASR Regulation

• Preamble of November 21, 1997, Final Rule relating to the Classification of ASRs

• “FDA believes that clinical laboratories that develop such [laboratory-developed] tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction under the act. However, FDA recognizes that the use of [laboratory] developed tests has contributed to enhanced standards of medical care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health. For these reasons, FDA declines to accept the suggestion that all [laboratory] developed tests be classified as Class II or III medical devices.”

• FDA denied my firm’s citizen petition on August 12, 1998
Enforcement Discretion

• For years, FDA has taken the position that LDTs are medical devices but that it will generally exercise enforcement discretion.

• Examples of enforcement:
  – Warning Letter to LabCorp (Sept. 29, 2008)
  – Warning Letter to EXACT (Oct. 11, 2007)
  – Untitled Letters to various direct-to-consumer tests
  – Warning letter to 23andMe, Inc. (Nov. 2013)
2010: FDA Announces Plan to More Actively Regulate LDTs

• FDA announced in June 2010 that it was revisiting this years-long policy of exercising enforcement discretion over LDTs

• FDA held a public workshop to discuss the issue in July 2010

• FDA officials subsequently indicated that the agency was developing a plan to more actively regulate LDTs under a risk-based framework, to be issued as draft guidance
FDA Proposed Framework for Actively Regulating LDTs

• Congress concerned about FDA regulation of LDTs
• Food and Drug Administration Safety and Innovation Act (FDASIA) required FDA to notify Congress at least 60 days before the agency issued a draft guidance document or regulation regarding LDTs
• July 31, 2014 – FDA provided Congress with Notice and copies of two draft guidance documents
  – Notice provided day Congress left for recess
• October 3, 2014 – FDA formally issues two draft guidances in *Federal Register*
Draft Guidance Documents

- “Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)” (Framework Guidance)
- “FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)” (Notification Guidance)
- LDT defined as “an IVD that is intended for clinical use and designed, manufactured and used within a single laboratory”
  - Definition includes modifications of FDA-cleared or approved tests, e.g., digital pathology, by laboratories
  - Not clear how much of a modification would convert test into an LDT
- Proposal likely also will affect manufacturers of products labeled as research use only (RUO)
Open Question Related to Pathology

- Are anatomical pathology services using a digital pathology product subject to regulation as an LDT?
  - Examples include histopathology or surgical pathology, cytopathology, and hematology
  - ACLA written congressional testimony: “It is difficult to see how the FDA could consider a pathologist reviewing a slide as an in vitro diagnostic or an LDT; in this instance, the pathologist is practicing his or her field of medicine just as any other physician when practicing medicine in his or her office. However, the Agency has written the anticipated details of the draft guidance so broadly that they appear to sweep into the risk-based framework any procedure a laboratory performs that is intended for clinical use and is not an unmodified FDA-approved or -cleared test kit, unless specifically excepted.”
  - FDA’s definition is extremely broad
Framework Guidance

• Risk-based approach to regulation
• Three groups of LDTs
  – No regulation (enforcement discretion)
  – Partial regulation (partial enforcement discretion)
  – Full regulation
LDT Group 1 – Enforcement Discretion

• Type of LDTs
  – LDTs solely for forensic (law enforcement) purposes
  – Certain LDTs for transplantation when used in CLIA-certified, high-complexity histocompatibility laboratories

• Regulatory Requirements
  – Will not be required to comply with FDA regulation (e.g., establishment registration and premarket submission)

• These exemptions are narrow
LDT Group 2 – Partial Regulation

• Type of LDTs
  – Low-risk LDTs
    • Equivalent to class I devices
  – LDTs for rare diseases
    • Perform fewer than 4,000 tests per year
    • Some tests are for rare conditions involving testing tens of thousands of people to find single patient
LDT Group 2 – Partial Regulation (cont’d)

• Type of LDTs
  – Traditional LDTs
    • The type of LDTs that were available in 1976
    • LDT must be comprised of components and instruments that are legally marketed for clinical use – no RUO or IUO
      – This limitation likely will affect manufacturers of products labeled as RUO
  – LDTs for Unmet Needs
    • For which there is no FDA-approved or cleared device for the same intended use available at the time the LDT is launched or afterwards
    • Commercial implications for digital pathology
LDT Group 2 – Partial Regulation (cont’d)

• Regulatory Requirements
  – Notification
    • Alternative to establishment registration and device listing
    • No tax – since device listing triggers tax, “notification” avoids tax
  – Medical Device Reports (MDRs)
    • Report adverse events (death, serious injury and malfunctions that could lead to the same) to FDA within defined timeframes
    • Will need to establish MDR procedures
  – NO Premarket submission
  – NO compliance with Quality System Regulation
LDT Group 3 – Full Device Regulation

• Type of LDTs – High and Moderate Risk tests
  – Highest Risk
    • LDTs with the same intended use as a cleared or approved companion diagnostic
    • LDTs with the same intended use as an FDA-approved class III device
    • Certain LDTs for determining safety and effectiveness of blood or blood products
  – Other High Risk
    • Those classified as class III devices
  – Moderate Risk
    • Those classified as class II devices
• LDTs of these types will be grandfathered until a premarket submission is required
LDT Group 3 – Full Regulation (cont’d)

• Regulatory Requirements
  – Notification
  – MDR Reporting
  – Recall Reporting
  – Premarket submission
    • PMA or 510(k), as applicable
  – Compliance with Quality System Regulation
    • Only after PMA is submitted or 510(k) clearance is obtained
Proposed Implementation Timing

• 6 Months
  – All labs must notify FDA of their LDTs
  – Adverse event reporting for LDTs begin

• 12 Months to year 5
  – Premarket submission for High Risk LDTs phased in
  – Not clear how phasing will occur
  – Grandfathering applies only to LDTs that are on the market when final guidance issued

• Years 5 through 9
  – Premarket submission for Moderate Risk LDTs phased in
Additional Challenges to FDA Statutory Authority

- Washington Legal Foundation’s Sept. 2006 and American Clinical Laboratory Association (ACLA) June 2013 citizen petition challenge FDA authority to regulate LDTs
- On July 31, 2014, the same day as it provided notification to Congress, FDA rejected the WLF and ACLA petitions
- Genentech had petitioned FDA in December 2008 to, among other requests, take action against companion diagnostic LDTs
  - FDA responded to Genentech petition on July 31, 2014. FDA denied some of the specific requests but noted that the proposed framework would accomplish many of the petition’s goals
Statutory Argument

• FDA’s authority extends to “devices” – LDTs are know how – not “devices”
• Congress intended for CLIA to be the single authority under which LDTs are regulated
• Commercial distribution element is missing
Guidance vs. Notice-and-Comment Rulemaking Argument

• Under Administrative Procedure Act (APA), FDA must issue notice-and-comment rulemaking before making substantive rules

• Protections in rulemaking not included in guidance
  – FDA must respond to each comment in the preamble of final rule
  – Economic Impact Analysis
  – Regulatory Flexibility Analysis
Notice-and-Comment Rulemaking (cont’d)

• Argument: Agency cannot avoid notice-and-comment rulemaking requirements by claiming that a major change is merely an interpretation of an existing obligation
FDA Resources

• Where will FDA get resources to implement framework?
• FDA has indicated that it will seek user fees for labs in next round of medical device user fee negotiations
• Possibility of bottleneck and application queue
Duplication with CLIA

• Duplication with several aspects of CLIA scheme
  – Analytical validation
  – Inspections
  – Quality System Regulation
  – Role of CLIA validation
Modifications to FDA cleared or approved tests

• FDA states in framework guidance document: Any modifications to “an FDA cleared/approved device in a way that affects device performance or intended use is considered to be a device manufacturer... [and] [t]hese modified devices must meet premarket submission requirements”

• On September 10, 2014, Alberto Gutierrez, Director of the Office of In Vitro Diagnostics and Radiological Health at CDRH stated at an American Association of Clinical Chemistry webinar, that if the laboratory modifies the assay enough to believe the modification requires validation, then it becomes an LDT
Other Concerns

• Regulatory LDTs will harm innovation
• Regulatory LDTs will diminish access to tests for rare or emerging diseases
• Inhibits rapid incorporation of new technology or knowledge
• Cost to health care system
• No need for regulation
Arguments for Regulation

• Statutory authority exists
• LDTs have evolved, and regulatory requirements need to as well
• LDTs pose risks; FDA oversight is needed
• Need level-playing field
• Hampers development of companion diagnostics
• Having two parallel systems is not rational or fair
What’s Next

• Important to remember...
  – These are proposed draft guidance documents
  – Even if they are finalized, they will not be legally binding
    • Guidance documents do not create any legal obligations
  – However, they would establish FDA’s current interpretation of the law
What’s Next

• Congress could theoretically block the issuance of the guidance, but unlikely
• There are already groups on both side of these documents:
  – Favor FDA regulation
  – Favor existing CLIA regulation
• FDA has indicated that it will hold a public meeting this week (October 23) to discuss the proposed draft guidance documents
• CMS/CDC meeting on November 4-5 in Atlanta Georgia (webcast will be available)
• FDA has indicated that it will also hold a public meeting in early January 2015 to collect additional input during the comment period
Many Open Questions

• We expect there to be many comments. There are many open questions in the proposed drafts. For example:
  – How will risk be determined?
  – Will FDA identify what group an LDT falls into or will laboratories self-identify?
  – Clarify definitions of LDT types
  – Timing of draft guidance regarding definition of class I, II and III LDTs
  – What will constitute a malfunction for reporting purposes?
Comment Period

• A 120-day comment period, ending January 30, 2015
• FDA specifically requests public comment on the following topics in the Framework Guidance:
  – Whether the healthcare system criterion in the Traditional LDT and LDT for Unmet needs can be omitted
  – Standard for determining if an LDT is for a Rare Disease (e.g., use of the <4,000 standard) or an alternative standard
  – Quality System Regulation phase-in timeline
  – Notification – whether a single notification from a healthcare system is sufficient if the test is being run in multiple labs and whether some LDTs should not require registration and listing
Long Road Ahead

• FDA’s formal issuance of the draft guidances is just the start of the process

• There will be much debate over what the ultimate regulatory framework should look like (if any)
  – Already drawn criticism from some members of the House Committee on Energy and Commerce Subcommittee, and support from some organizations, and opposition from others

• We do not expect that the draft guidance documents will be the final version (if one is issued)
Long Road Ahead (cont’d)

• Final guidances will need to undergo review by Health and Human Services (HHS) and The Office of Management and Budget (OMB)

• Expect legal challenges to the guidances once they are finalized