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The Changing Regulatory and Policy Environment for In Vitro Diagnostics

James A. Boiani

Senior Counsel

Epstein Becker Green

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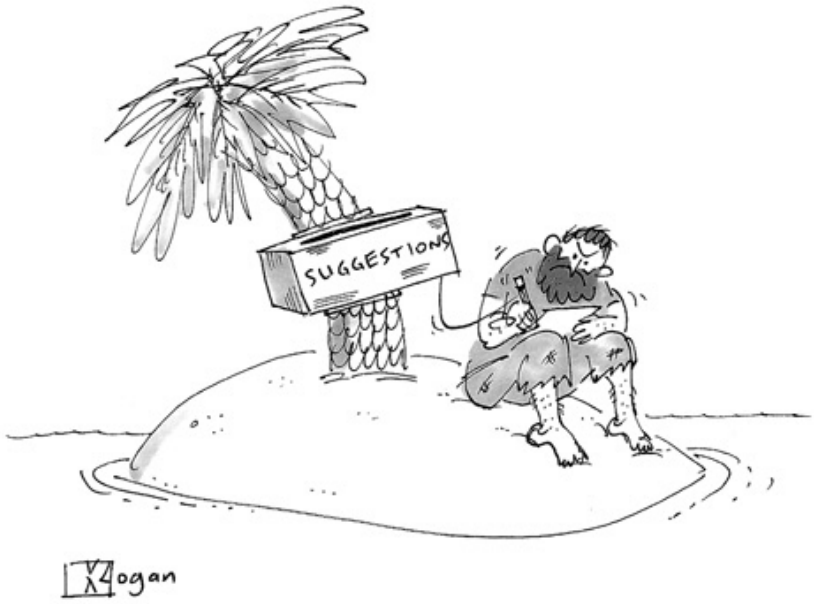
- The opinions expressed herein are my own.



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Lots to Cover Today

1. Recent Diagnostics Guidances
   - RUO/IUO Guidance
   - Molecular Diagnostics with Combined Functionality
   - Multiplex Testing
2. Companion Diagnostics
   - Needed Guidance & Pending Legislation
3. Faster Ways to Market
   - Laboratory Developed Tests
   - Transitional IVDs
   - Emergency Use Authorizations
4. Guidance fostering scientific exchange
   - Good Reprint Practices & Unsolicited Requests
5. CLIA Waivers
6. Other things to keep an eye on

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1. Recent Diagnostics Guidances

- RUO/IUO Guidance
- Molecular Diagnostics with Combined Functionality
- Multiplex Testing

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Draft RUO/IUO Guidance

- Draft Guidance released in June 2011
- The draft was controversial because of expansive reading of intended use
  - Tied intended use to actual customer use: Manufacturer was to halt sales if it "had reason to know" RUO product was used in LDT by customer
  - Created significant barriers to communication between manufacturer and customers
- Stakeholders voiced policy and legal concerns during comment period, and FDA listened

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Final RUO/IUO Guidance

Issued Nov. 2013, and incorporates many changes

- Removed the "knows or has reason to know" standard
- Adds the concept of a customer certification
- Does not speak to halting RUO/IUO sales
- Recognizes manufacturers can provide "generic" technical support related to RUO/IUO uses

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Thoughts: Marketing RUO/IUO

- Expect continued focus on intended use determined by the totality of evidence
  - An RUO/IUO certification that is known to be inaccurate may not hold up
- Create clear policies governing support that will be offered for RUO/IUO products
- Make sure labeling is clean
  - Clear RUO/IUO statements
  - No language undercutting those statements

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Outstanding RUO/IUO Issue

- What about RUO/IUO that have been used for many years and have become standard of care?
  - Issue raised in comments.
  - Will FDA exercise enforcement discretion and encourage submission of applications?
    - A similar approach has been used successfully for unapproved drugs.

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Combined Functionality: MolDx Guidance

- *Molecular Diagnostic Instruments with Combined Functions* (Draft, Apr. 2013)
- FDA policy on marketing molecular diagnostic instruments with
  - FDA Approved/Cleared Functionality +
  - Other Functionality (RUO, IUO… Class I-Exempt?)
- Builds on past informal advice

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Takeaways from MolDx Guidance

- Prospective and retrospective application
  - "FDA intends for you to address" division of functionalities "in any new premarket submission" for an existing PMA/510(k)
- **Separate** functionality
  - Separate user interfaces, separate labeling… separate anything that *might* suggest un-cleared/un-approved functionality *is* cleared/approved
  - Do recommendations go to far? To burdensome?

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Takeaways from MolDx Guidance

- Ensure additional functionalities do not interfere with cleared/approved uses
- Third party assay makers are affected
  - "Assays submitted to FDA by third party assay developers. . . will be reviewed by FDA on a case-by-case basis to determine whether risks are adequately mitigated"
  - Will assay developers need to create their own separation controls?

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Takeaways from MolDx Guidance

- MDRs
  - "FDA expects malfunctions, injuries, and deaths associated with [un-cleared/un-approved] functions to be reported"
  - How does this jibe with RUO policies, i.e., if a product is not intended for clinical use under what conditions would it produce an MDR event?
    - Limited to RUO functions that impact IVD use?
    - Would clinical use of RUO product be a 'malfunction?'

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Takeaways from MolDx Guidance

- Why is the guidance limited to molecular diagnostics?
  - Shouldn't there be a new comprehensive policy for all IVDs (or devices) with dual uses?

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Thoughts:
Addressing MolDx Guidance in submissions

- Always go back to the two fundamental issues –
  - **Intended Use**: Separation is about ensuring that uncleared/unapproved uses are not represented as cleared/approved
  - **Interference**: Don't let unapproved/uncleared uses interfere with cleared/approved functions
- There are many ways to address these issues
  - Remember, guidance is *not* law
  - If recommendations in the guidance are not practical for a particular product push for something that works

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Multiplex Systems

- FDA Draft Guidance, *Highly Multiplexed Microbiological/Medical Countermeasure in Vitro Nucleic Acid Based Diagnostic Devices* (Nov. 2012)
  - Provides "recommendations for studies to establish the analytical and clinical performance of highly multiplexed microbiological/medical countermeasure *in vitro* nucleic acid based diagnostic devices (hereafter referred to as HMMDs) intended to simultaneously detect and identify [≥20 different organisms/targets from] nucleic acids extracted from a single appropriate human specimen or culture. For the purposes of this draft guidance document, the multiplex level that is used to define HMMDs is the capability to detect."

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Multiplex Systems

- There are many specific recommendations in the 32 pages of guidance
  - Significant cost concerns
  - Requests submission of design inputs and outputs with premarket submissions
    - Is this an over-step? Design I/Os are required as part of the quality system, not for 510(k) submissions
- Is this level of specificity what guidances should strive for?
  - Would it be better to create more general guidance on principles of multiplex test development?
  - Address important specifics with a short guidance?

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2. Companion Diagnostics

- Needed Guidance
- Pending Legislation (MODDERN Cures Act)

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Companion Diagnostics (CDx)

- October 2013 FDA Personalized Medicine Report Re-affirmed FDA commitment to personalized medicine & CDx
- There have been recent approvals of CDx, but this is an area where stakeholders have been asking for guidance

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CDx Guidance – Why is it needed?

- Improving cross-Center uniformity
  - CDRH, CDER, and CBER may not always see eye-to-eye on clinical utility, and other issues
- Addressing important specifics
  - Selection of biomarker +/- subjects
  - Marker(s) selection
  - Claims about markers with probable value

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CDx Guidance

- FDA has been developing a guidance of co-development of drugs and diagnostics, but release date is unclear
  - Not clear if it will address anything about diagnostic development *outside* of co-development guidance
- For the time being, there is some useful conceptual information in FDA's enrichment guidance
  - *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (Draft, Dec. 2012)

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MODDERN Cures Act (H.R. 3116/3091)

- Objectives
  - Advance diagnostics
  - Encourage research on “dormant therapies”
- Geared toward companion diagnostics
  - Finding: “Advanced and innovative diagnostic tests have the potential to dramatically increase the efficacy and safety of drugs by better predicting how patients will respond to a given therapy.”
- Lead Sponsor: Lance Leonard (NJ-7)

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MODDERN Cures Act (H.R. 3116/3091)

- Section 101 – Establish "Advanced Diagnostics Education Council"
  - Create a standard terminology guide for IVDs
  - Comprised of Agency officials (FDA, NIH, CDC, etc.), CMOs/CSOs of patient advocacy organizations, and other experts
- Section 102 – Incorporates reimbursement changes

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MODDERN Cures Act (H.R. 3116/3091)

- Section 103 – Promoting development of innovative diagnostic tests
  - Developed by or with participation of a therapeutic developer; and
  - Demonstrated through valid scientific information (e.g., peer-review lit.) to –
    - Improve identification of patients who should/not get the therapeutic (Companion Dx); or
    - Detect a FDASIA "qualifying pathogen"

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MODDERN Cures Act (H.R. 3116/3091)

- Developing a Dx can add time to therapeutic market exclusivities (e.g., Hatch-Waxman exclusivity)
  - 12 months for co-developed diagnostic
  - 6 months for otherwise-developed diagnostic
- Could be used twice for the same drug
  - Once per indication
- Dormant Therapy – Encourages development of therapies that otherwise go undeveloped due to weak or no patent protection by offering 15 years of market exclusivity.

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Faster Ways to Market

- Laboratory Developed Tests
- Transitional IVDs
- Emergency Use Authorizations

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Laboratory Developed Tests

- June 2012 ACLA Citizen Petition asking FDA to recognize LDTs are not IVDs
  - FDA responds it "has been unable to reach a decision on [the] petition because it raises issues requiring further review and analysis by agency officials."
  - FDA has asserted authority to regulate LDTs under the 1976 Medical Device Amendments . . . after 38 years, will FDA regulation ever come to LDTs?

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Laboratory Developed Tests

- Recent activity
  - 23andMe warning letter
    - Direct-to-consumer test
    - Argues LDT exemption does not apply
  - Illumina's MiSeqDx is cleared to further development of genome-based LDTs
- Commissioner Hamburg explained in NEJM piece following MiSeqDx clearance that there is still work to be done toward regulation
  - FDA is not giving up, but when will it act?

Proposal
Moving Forward - Refocus the Discussion

- We don't talk enough about the **fundamental problem**, which is **unequal regulation**
  - LDTs are IVDs are both diagnostics run by a CLIA laboratory to provide clinical data
  - Why are manufacturers required to do so much more than a lab to bring a test to market?
- *This* should be the impetus for immediate change

Development of Diagnostics

Device Manufacturer

Clin. Laboratory

Pathway for FDA-approved IVD

Pathway for CLIA-Validated LDT

Patients

FDA Regulation

CLIA Regulation

Laboratory Developed Tests

- The current dual system is not good policy
  - Either overburdens IVD manufacturers or under-regulates labs
  - Indirect regulation of labs *through* manufacturers
  - Limits scientific discourse between labs and IVD
- The current dual system raises legal questions
  - Is different treatment of labs and manufacturers "arbitrary and capricious"?
  - Are speech restrictions on, e.g., ASRs, narrowly tailored to meet 1st Amendment standards?

Laboratory Developed Tests

- When refocused, it is clear that FDA can address the issue by regulating LDTs **or** de-regulating IVDs
  - ACLA's petition highlighted FDA regulatory burdens that could hinder access to innovative diagnostics for small populations
  - FDA itself has recognized that systems could be improved to bring innovative new diagnostics to market more quickly

Transitional IVDs

- FDA has recognized the issue and is working on a solution
  - "We ensure devices are safe and effective, and that's protecting public health. . . *But we also have to promote public health, ensuring that there's timely access to those technologies, and facilitating innovation.*"
  - "A safe and effective technology may take longer to get to U.S. patients [than O.U.S. patients], and that's contrary to what we are about.
- FDA's answer: A TIVD framework
- MDUFA III commitment to develop TIVD path for emerging diagnostics makes this a priority

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Emergency Use Authorizations

- Emergency Use Authorization (EUA) : Allows marketing of unapproved products, or unapproved uses of approved products for "medical countermeasures"
  - 2004-13: Actual emergency required
  - 2013: Congress makes major amendments through Pandemic and All-Hazards Preparedness Reauthorization Act of 2013

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Emergency Use Authorization

- The new law gives FDA more flexibility to use EUAs
  - based on "a public health emergency, or a significant potential for a public health emergency";
  - that affects or has "significant potential to affect national security or the health and security of U.S. citizens living abroad"; or
  - is related to chem/bio/nuclear agent "or a disease or condition that might be attributable to the agent."
- Should FDA read the law broadly?
  - What poses the greater public health emergency: cancer or flu?

Question

FDA has recognized the need to "loosen the reigns" to spur innovation. Congress has also seen the need for flexibility.

- Is it time to look for a "grand bargain?"
  - Create a more efficient, less burdensome pathway for diagnostics, and
  - Bring IVDs and LDTs under one roof, all at once?

4. Guidance fostering scientific exchange

- Good Reprint Practices
- Unsolicited Requests

Updates to Good Reprint Practices

- FDA issued a revised Good Reprint Practice Guidance in Feb. 2014
- Basic concept remains the same
  - You can *proactively* disseminate certain kinds of literature discussing off-label use of your product
  - Only applies to high quality publications, and includes lot of bells and whistles regarding how information is transmitted
- Significant change in new draft
  - Extends GRP explicitly to clinical practice guidelines

Clinical Practice Guideline GRPs

- CPG must be from "trustworthy source," meeting IOM standards for the same
- Dissemination must comply with similar requirements that reprints and text do, e.g.,
  - Note that off-label use is being discussed
  - Distribution apart from promotional activities
  - Accompanied by approved labeling (or cleared intended use statement, for 510(k))

Thoughts on GRPs

- FDA should be applauded for trying to develop a system that furthers scientific exchange, but could this be improved?
  - Is it too cumbersome?
  - Is the wall between sales and science needed?
- GRP revisions reference handling of unsolicited requests, which raises a question…
  - When will FDA finalize its Dec 2011 Unsolicited Request Guidance?

Unsolicited Requests

- Unsolicted requests are the peanut butter to the GRP's chocolate
  - GRP allows proactive dissemination of off-label science, but must be significantly vetted (e.g., peer-reviewed)
  - UR allows scientific bodies separate from sales & marketing to respond to unsolicited requests for off-label information
    - Can include broader kinds of information (e.g., internal studies)

Unsolicited Requests

- There were many concerns regarding FDA's definition of "solicitation" in the draft guidance.
  - For example, if a manufacturer encouraged patients to post videos on Youtube, and the videos discussed off-label use, questions spurred by the video are "solicited."
  - Should this really be considered solicited? As a practical matter, how do you manage this?

Unsolicited Requests

- The GRP suggests FDA may be taking a less restrictive approach with new addition
  - Says "[t]o the extent that the recipients of the scientific or medical journal article have questions, the sales representative should refer the questions to [the sales-independent] medical/scientific officer or department"
  - Providing the off-label information to the customer in this context does *not* appear to constitute solicitation.
- Is a revised unsolicited request guidance on the horizon?
  - Will it address this issue?

5. CLIA Waivers

- CLIA certificate of waiver labs play an increasingly important role in point-of-care medicine
  - Most physician office labs are CLIA-waived labs
  - Moving tests closer to POC is a good thing
- However, it is increasingly difficult to get a CLIA waiver from FDA for a new technology
  - Reports of "1000s of CLIA waived tests" you may see in articles are misleading. Most of these are products that are waived automatically by statute or regulation, not through FDA's waiver process
  - FDA only grants a handful of waiver requests per year.
- What's going wrong?

Law and Guidance in Conflict

- By law, CLIA waivers must be granted for procedures "employ methodologies that are so simple and accurate as to render the likelihood of erroneous results *by the user* negligible."
  - "By the user" was added by Congress in 1997 to clarify that CLIA waivers about the impact of the user on accuracy, not inherent device accuracy
- If "waiver" labs can run a test as well as a moderate/high complexity lab, a waiver must be granted

FDA got right in 2001

- Draft Guidance from 2001
  - "Based on the legislative history and language incorporated into FDAMA, we interpret "accurate" to mean test performance (i.e., *the test performs the same in the hands of untrained users [as] it does in the hands of laboratory professionals under realistic conditions*)"

FDA Got it Wrong in 2005/8

- 2005/8: FDA publishes a new draft, then final, guidance that abandons the legislation
  - "[W]e use the term "accurate" tests to refer to those tests that are comparable to a traceable [i.e., gold standard] method, in which the results of measurements can be related to stated references."
  - This brought us back to the old system Congress had tried to fix in 1997

The numbers…

CLIA Applications	Under Old System that Prompted 1997 Law	Under the 2008 Final Guidance
Approved	12	15
Denied	8	16
Average Review Time	34 weeks	32 weeks
Longest Review Time	90 weeks	106 weeks

Things are getting worse, not better

Other Problems with CLIA Waivers

- FDA Guidance Documents on Blood Glucose Monitoring Systems for Home Use and Professional Use (2014)
  - Approach disables automatic CLIA waivers for home use monitoring by requiring labeling that expressly prohibits in professional environments
  - Is this the first of many assaults on home use automatic waivers?

Other Problems with CLIA Waivers

- New CLIA Categorization Guidance (2014)
  - Adds new MDUFA goals for CLIA waivers ranging from 180-330 days
  - Does not fix any fundamental problems with the system

6. Other Items on the Radar

- FDASIA Report on 510(k) Change Guidance
  - Required by Congress in response to concerns about changes to 1997 Guidance
  - FDA concludes overall framework to stay intact
- Final Presubmission Guidance
  - "CDRH and CBER intend to commit to the advice provided during these pre-submission meetings unless the circumstances sufficiently change such that our advice is no longer applicable"
  - What about CDER?

Protecting Access to Medicare Act of 2014

- Pegs Medicare pricing to market prices
  - 1-yr reviewed for "advanced diagnostics" (certain multi-plex LDTs)
  - 3-yr review for other tests
  - Takes effect in 2017
- Heads of planned payment reductions and repeals CMS plan to evaluate lab technology

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Questions?

- Questions, comments, and complaints can be sent to jboiani@ebglaw.com