EPSTEIN BECKER GREEN

Regulatory & Legal Oversight of IVDs and LDTs: Consideration of Proposed Solutions

Bradley Merrill Thompson
Epstein Becker Green and
the Combination Products Coalition

February 27, 2013

LDTs are IVDs

- LDTs are IVDs, as both are –
  - Intended for use in diagnosis of diseases or other health-related conditions
  - Used to analyze human samples out of the body
  - Performed using instruments, reagents, etc.
- They are regulated differently because of *who* writes the instructions for use… but if the two products are the same, shouldn't they be regulated the same way?
  - Both regulatory approaches *can't* be right

Comparison of Current Requirements

Requirements	IVDs (held to FDA standards)	LDTs (held to CLIA standards)
Premarket Review & Approval for Tests	Yes, for higher risk tests	No
Manufacturing tests under a Quality System, e.g., • Design Controls • Process controls • Complaint Handling	Yes	No
Reporting adverse events	Yes	No
Annual reports	Yes, for higher risk tests	No
Establishing clinical validity before using test	Yes	No*
Establishing clinical utility before using tests	Yes, as needed	No
Regulation of test performance claims	Higher Standards (FDA and FTC requirements)	Lower Standards (FTC only)

**** Laboratory directors must assure tests are of sufficient quality for use in patient care, but there is no evaluation of clinical validity along the lines required by FDA***

AdvaMed Proposal

- FDA reviews both IVDs **and** LDTs, applying the same standards to each
- Would leverage existing science to reduce premarket FDA regulatory requirements based on risk and familiarity with technologies & science
  - The higher the risk the greater the requirements
  - The greater the novelty of a test technology or science of a biomarker, the greater the requirements
  - Companion diagnostics would likely be subject to the highest standard of regulation due to risk and (potentially) novelty
- Calls for harmonizing premarket and post-market requirements for IVDs and LDTs

ACLA Proposal

- LDTs continue to be subject to different review requirements than IVDs
- Augments the existing CLIA framework
  - Requires premarket notifications which include clinical validity data
    - Labs can use tests right away after submitting notification
    - CMS can prohibit use if clinical validity is not established and there is an immediate risk to health
  - Requires adverse event investigation and reporting
  - Builds a registry to collect information on tests

Comparison of Proposals

Requirements	AdvaMed*	ACLA
Equal treatment of LDTs an IVDs under review	Yes	No (LDTs remain subject to less regulation)
Premarket Review/ Approval for Tests	Yes, for higher risk tests	No
Manufacturing tests under a Quality System	Yes	No
Establishing clinical utility before using tests	Yes, as needed	No
Establishing clinical validity before using tests	Yes	No^
Annual reports	Yes, for higher risk tests	No
Reporting adverse events	Yes (Deaths, serious injuries *and* malfunctions)	Limited (Deaths and serious injuries only)
Regulation of test performance claims	Higher Standards (FDA and FTC requirements)	Lower Standards (FTC + disclosing test limits)

**** Leverages existing information to reduce pre-market regulatory burdens***

^ Some clinical validity data are collected, but not subject to agency review before the test is used

Risk Associated with CDx

- CDx have generally been developed to guide therapies in treating serious or life-threatening diseases (e.g., cancer).
  - In these situations, there are serious safety concerns, making it important to get the CDx development right.
  - An inaccurate test could lead to withholding life-saving treatments, or providing a drug with serious side effects to a patient.
- How much oversight is required to protect the safety of patients?

Is the LDT or IVD Pathway Better for CDx?

- Safety and effectiveness of high-risk CDx can only be assured by adequate studies
  - Inadequate studies pose risks to patient safety
- The issues associated with these studies involve very complex scientific questions
  - Manufacturers work extensively with FDA on a case-by-case basis to answer these questions so they can determine what is needed scientifically to support safety and effectiveness
- In light of the complexities and risks involved –
  - Does the LDT approach, which gives an individual lab wide latitude to develop tests on its own with minimal oversight, provide adequate protection of the public health, **or**
  - Should the IVD approach, which calls for collaboration on study design with, and pre-market review and approval by, FDA be used?

Development of CDx

Device Manufacturer

Clin. Laboratory

Pathway for FDA-approved IVD

IVD Kits

Pathway for CLIA-Validated LDT

ASRs GPRs

LDT

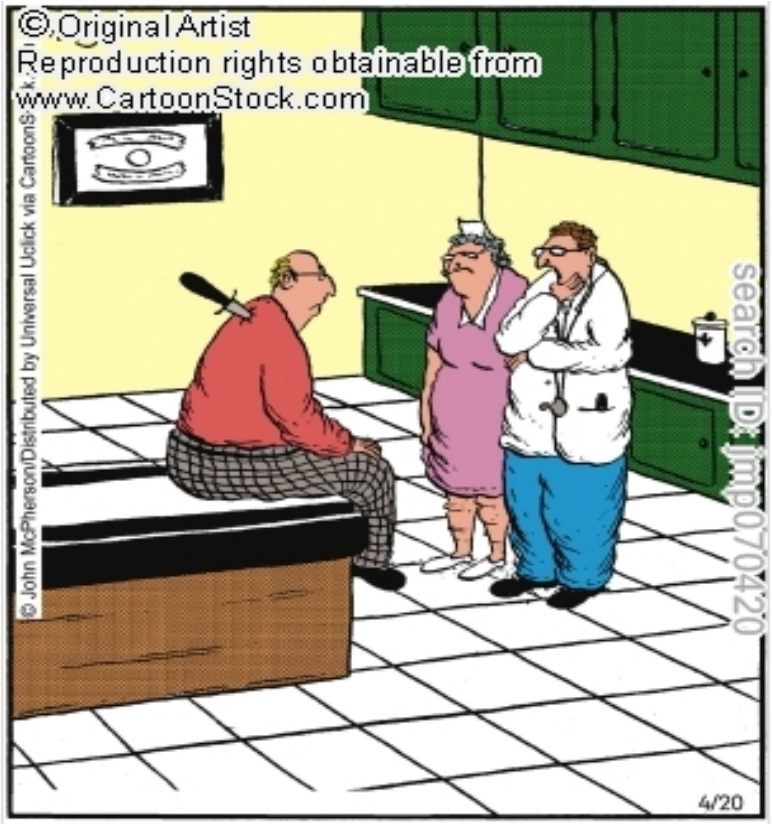
Patients

FDA Regulation

CLIA Regulation

Denotes Innovation

Sometimes we miss the obvious…



"You say it's a sharp, stabbing pain. Hmmmm ... sharp ... stabbing pain."

If IVD and LDT data serve the same purpose, and the only difference between them who develops the diagnostic, what is the sense of two different regulatory systems?

Conclusions

- The current system needs to be reformed
- Whatever system is adopted needs to apply equally to both IVD manufacturers and laboratories, commensurate with risk
  - Elements of both proposed systems have appeal, but given the potential risks associated with companion Dx, rigorous but streamlined FDA requirements along the lines of AdvaMed's proposal seem most desirable to protect patients
- Although working with FDA on a case-by-case basis assures CDx study designs are adequate, substantially more guidance is needed to make CDx development more efficient and promote innovation