The Changing Regulatory Environment

What to Expect in 2011 and Beyond

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Topics

- Policy Landscape 2011 – 2012
- FDA Regulation of LDTs and IVDs
  - AdvaMed Risk-Based Approach
  - Hatch Bill
- Outlook

112th Congress – Overview

- New Congress, lots of new members
- Most legislative activities focus on
  - Jobs and the Economy
  - Budget and Federal Deficit
- Health Care Reform still a hot topic
  - Medical Device Tax?

112th Congress - Overview

- Genomics and Personalized Medicine Act – H.R. 5440 from the 111th Congress (Rep. Anna Eshoo)
- GAIN Act – H.R. 6331 in the 111th Congress – Generating Antibiotic Incentives Now
- National Health Council proposal for Personalized Medicine
- FDA User Fee Reauthorization (MDUFA)

What the Concerns over LDTs?

- FDA enforcement discretion is now a loophole
  - Vast majority of tests for genetic conditions are LDTs
  - The rise of IVD Multivariate Index Assays (IVDMIAs) using complex “black box” computer algorithms
  - Business models leverage enforcement discretion to provide more rapid market access
  - LDT and IVD risks are the same, no matter the business model

Evolving FDA Landscape

- AdvaMed Risk Based (RB) Approach for regulation of all diagnostics draft guidance submitted to FDA (4/10)
  - No legislative change needed
- FDA announces plans to regulate LDTs
  - Key aspects of AdvaMed's RB Approach cited in FR notice (6/10)
  - AdvaMed testifies at FDA LDT oversight hearing (7/10)
  - AdvaMed expanded written comments to docket (9/10)
- FDA announces forthcoming plans for LDT registration and risk based oversight framework (11/10)

AdvaMed Risk-Based Approach

- Built on historical FDA precedents and international risk management standards*
  - Exempt additional low risk Class I/II diagnostic tests from premarket reviews
  - Align intensity of 510(k) reviews with patient risks, novelty, user and risk mitigations (Tier-Triage)
  - Can be implemented without legislation

* FDA DCLD 1996 Tier/Triage Guidance FDAMA ’97 Class I/II Exemptions, and ISO 14971: 1997

AdvaMed Risk Based Approach

Risk*

-Clinical use of device

-Novelty of analyte

-Novelty of technology

-Training of operator

Risk Mitigation

-Scientific evidence

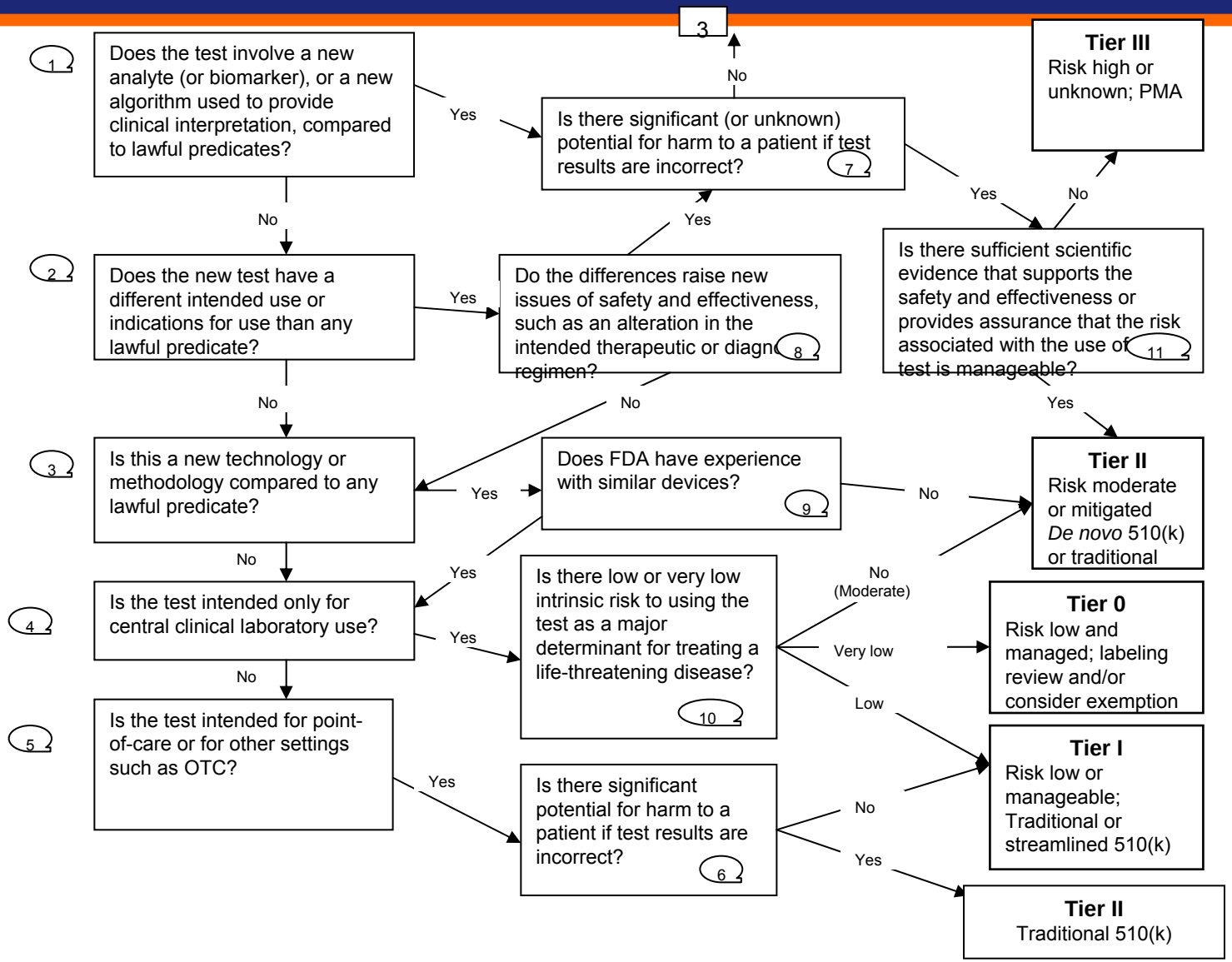
-General/special controls

-Laboratory controls

-User experience

*Risk is intrinsically higher for novel tests used as major determinant of treatment

Tier-Triage Flowchart



Tier Assignments

Tier Assignments	Risks and Mitigations	Submission Type
Tier 3	Risk high or unknown	PMA
Tier 2	Risk moderate and/or mitigated	*De Novo* or Traditional 510(k)
Tier 1	Risk low and manageable	Traditional 510(k) or Streamlined 510(k) Labeling Review
Tier 0	Risk low and mitigated	Streamlined 510(k) Labeling Review or Candidate for Exemption

Hatch “BETTER” Proposal for Regulation of Dx

- **“Better Evaluation and Treatment Through Essential Regulatory Reform” from the Office of Sen. Hatch (R-UT)**
  - Draft bill creates a new regulatory category – In Vitro Diagnostic Products (IVDP)
  - Originally focused on “Advanced Personalized Diagnostics (APDx) ”, not all tests
  - Latest draft bill includes all LDTs and IVDs
  - Maintains CLIA lab quality oversight for lab practices

“BETTER” – Dx Removed from Device

- Section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) is amended—
  - (1) in subsection (h)—
  - (A) by striking “in vitro reagent,”; and
  - (B) by adding at the end the following:
- “The term „device‟ does not include in vitro diagnostic products, as defined in section 575(6).”;
  - (2) by adding at the end the following: 2
- “(ss) the term „in vitro diagnostic product‟ or „IVDP‟ has the meaning given such term in 3 section 575(6).”.

IVDPs treated in same manner as devices for MDRs, GMPs, etc, via cross-reference - but shielded from device tax

BD

“BETTER” Fast Track and Other Streamlined Processes

- Shorter FDA review timelines for premarket review
- Fast track process for certain tests, including biomarker qualification (i.e., unmet needs or significant improvement re. serious disease)
- Increased flexibility in labeling for new indications for companion tests (i.e., medical literature or medically accepted indication)
- Allows postmarket modifications of tests resulting in new claims in many cases without premarket review

“BETTER” Elements of Risk-Based Approach

- Creates ongoing exemptions process
  - for well standardized and low risk tests from premarket review
- Calls for risk based guidance that
  - outlines types of risks and mitigations to be considered in determining the content of submissions
  - improves overall transparency and predictability in review process

“BETTER” Review Standard

- Use of ‘competent and reliable’ standard based on claim and risk associated with test—not ‘safe and effective’
- Considers cost to substantiate the claim and feasibility to conduct additional studies
- Consistent in many respects with current review standard
- Clinical validity not explicitly required for all tests under proposal, but FDA has discretion

“BETTER” Treatment of Existing LDTs

- Grandfathering of LDTs approved by NYS Department of Health
- Grandfathering of most other LDTs (unless specific public health threat notice published in Federal Register)
  - Maintains FDA authority to act, but presumption of grandfathering

“BETTER” Treatment of Off-label Promotion

- Similar to FDCA—advertising or promotion (including labeling) prohibited for unapproved claims

- More permissive, however, in several respects:
  - All submitted claims approved or otherwise will be referenced in IVDP databank
  - FDA may issue statement regarding certain off-label uses (i.e., to promote transparency and innovation, for discussion between lab director and physician)
  - May disseminate published, peer-reviewed off-label information subject to FDA limitation

“BETTER” Summary of Advantages

- FDA oversight of all diagnostics tests, including LDTs
- Preserves many aspects of FDCA
- Exemptions for many low risk tests
- Integration of several aspects of Risk-Based Approach
- Shorter FDA review timelines for premarket review
- Increased flexibilities, such as labeling, modifications, and references to off-label information
- Lays groundwork for value-based reimbursement

“BETTER” Drawbacks

- Legislation required; open to many changes
- Significant disruption (cost and complexity) for manufacturers to convert to new requirements despite efforts to minimize
- Lack of certainty regarding new rules to be promulgated following transition period
- Grandfathering of most LDTs
- Perception of lowering the bar?
- Need for additional conforming amendments
- FDA discretion/interpretation

Possible FDA Approach for LDTs

- **Risk-based approach starting with**
  - IVDMIAs
  - Companion diagnostics
  - Cancer diagnostics
- **Low risk tests exempt**
- **Registration and listing**
  - To determine universe of LDTs
- **Classification panels**
  - Groups of test classified all at once

What to Watch for In Dx Regulation

- **Response to FDA Regulation of LDTs**
  - Laboratories
    - Push for FDA regulation instead of guidance
    - Challenge FDA legal authority in court
    - Go to Congress for legislative remedy
  - Congress
    - Legislate new paradigm through MDUFA bill

Thank you!

Questions?