FDA Overview of Molecular Diagnostics and the Critical Path Initiative

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Medical Device Amendments of 1976

- All medical devices, including IVDs
- General controls
  - Registration and listing
  - Good manufacturing practices
  - Post market reporting
Premarket Review

- 510(k)-moderate risk
- PMA-high risk
- Administrative differences
- Common scientific base
Analytical Performance

- Accuracy
- Precision
- Analytical specificity
- Analytical sensitivity
Clinical Performance

- Analytical signals can be turned into clinical action
  - Diagnostic sensitivity/agreement
  - Diagnostic specificity/agreement
  - Predictive value of positive or negative results
Labeling -- 809.10(b)

- Intended use
- Performance characteristics
- Limitations
The Real World of Regulation

- FDA
- CMS (CLIA)
- CMS and others (third party pay)
Bad News: MolDx

- Cutting edge new technology -- multiplex, bioinformatics, nanotechnology
- Paucity of material or method standards
- Biological and clinical nuances
- Financial uncertainties
Good News: MolDx

- Regulatory trail is well lit
  - Literature, Standards, Guidances
- Broad menu of regulatory tools
  - Pre-IDE
  - Expedited reviews
  - Real time reviews
  - De novo classification
- Mandate to be least burdensome
- New scientific resources -- MDUFMA
- New regulatory programs -- OIVD data template, critical path, VGDS
Principle Road Maps

- STARD Initiative (Bossuyt, et al., 2003)
  - Standards for reporting Dx accuracy
- REMARK Initiative (McShane, et al., 2005)
  - Reporting recommendations for tumor marker prognostic studies
Growing FDA Guidance

- Voluntary Genomic Data Submissions guidance
- Concept paper on co-development
- Statistical guidance on IVD labeling
- Guidance on pharmacogenetic and heritable genetic tests
- Bayesian statistics
Review Successes: MolDx

- Cystic Fibrosis test – 109 days
- Avian flu – 14 days
- UGT1A1 – 9 days
- MammaPrint—30 days FDA time, ~140 days total
Laboratory developed tests

- “home brews”
- Broad menu of tests
- Wide range of risk
- Regulatory enforcement discretion
ASRs

- Recent draft guidance: “Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions”
- Growing issue of inappropriate marketing
- Clarification:
  - What is/is not an ASR
  - How ASRs can be marketed
IVDMIAs

- Recent draft guidance: “In Vitro Diagnostic Multivariate Index Assays”
- Class of test
  - Complex interpretation of multiple analyte signals
  - May be difficult to validate
  - Results have high patient impact
  - FDA not comfortable with enforcement discretion when home brew
IVDMIAAs

- Test reports classifier/score/index, “magic number” that predicts clinical outcome
- Created using empirical selection of multi-analyte “signature” from large number of signals, or by empirically weighting known features to match a given result
- No “prior knowledge” available to evaluate value of result, can’t second-guess result, interpretation not obvious
- Problem: Incomplete knowledge of underlying biological truth (could change as science progresses, consensus publications, etc.)
IVDMIAs

- Public meeting Feb. 8, 2007
- >300 attended, 31 presentations
- Opportunity to provide input
- Guidance not clear
- Both ends of spectrum and nearly everything in between
- Few proposals for moving forward
The Critical Path Initiative
Intersection of Drugs and Diagnostics
Critical Path Initiative
Critical Path Initiative

- Public-private partnerships
  - Success stories
  - Failures, roadblocks, bottlenecks
  - Missed opportunities

- New tools
  - Biomarkers
  - Trial designs
  - Modeling
  - Manufacturing

- Goal: better, faster, cheaper
Critical Path Initiative: IVDs

- Personalized medicine
  - Pharmacogenomics
- Biomarkers--two contexts “Today’s biomarkers are tomorrow’s diagnostics”
  - Diagnosis
  - Drug discovery
- Co-development
Critical Path Initiative

- Infrastructure
- Opportunities list
- Pilot programs
Co-Development

- If predictive diagnostic determines drug choice--safety and effectiveness of drug becomes hostage to diagnostic
- Need to understand system as a whole
Trial Design: Growing Literature

- Simon and Wang, 2006
- Pennello and Vishnuvajjala, 2005
- Sargent et al, 2005
- Pusztai and Hess, 2004
Predictive Marker: New Drug vs Conventional Tx

- Determine biomarker status; randomize therapy within biomarker categories (randomized block)

```
All ➔ Test biomarker ➔ Biomarker + ➔ New drug
     |                          |       |
     |                          |       |       |
     |                          |       |       |       | Conventional Tx
     |                          |       |       |       | New drug
     |                          |       |       |       | Conventional Tx
Biomarker - ➔ New drug
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Best treatment choices in each biomarker category
Most information about biomarker impact on drug outcome
Partial Marker: Biomarker for toxicity

- Determine biomarker status; randomize therapy within biomarker categories (randomized block)

All → Test biomarker

Biomarker + → New drug

Biomarker - → Placebo

Unethical to treat (+) for toxicity
Test not informative for AE risk; No sn/sp, PPV
Partial Marker: Biomarker for efficacy

- Determine biomarker status; randomize therapy within biomarker categories (randomized block)

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All → Test biomarker

Biomarker +

Biomarker -

New drug

Placebo

New drug

Placebo

Unethical to withhold new Tx if high expectation that biomarker predicts response
Get PPV,NPV, but not sn/sp
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**Predictive Marker: New Drug vs Conventional Tx**

- Determine biomarker status; randomize biomarker-selected therapy in one group, unselected therapy in other

If A>B, can’t tell if increased impact due to biomarker or new drug
No info on biomarker sn/sp, NPV; no info on drug in (-)
Predictive Marker: Enrichment/targeted design

- Determine biomarker status; randomize only in biomarker positive

Ethical concerns: known toxicity, predict response in poor prognosis
Don’t know whether (-) pts would benefit, can’t tell if drug performance is better in (+) compared to unselected population
Predictive Marker: Complete randomization

- Randomize by treatment; look back at biomarkers

All

New Drug → Biomarker tested → Biomarker +

Old drug/placebo → Biomarker tested → Biomarker -

Unequal allocation of +/- pts to different Tx, may require larger sample. Can be used when test not avail. at time of drug trial
Codevelopment

- Bad news
  - One size does not fit all
  - Integration of drug and Dx development cycles still uncertain
  - Progress is slow
Codevelopment

- Good news
  - Real advances being made
  - Interest is high
  - Pay-off large
FDA Mission

- Promote public health
- Protect public health
- Tension in objectives
Good Science