In Vitro Diagnostic Device Evaluation and Safety

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Disclosures

- None with respect to commerce.
- Personal opinions and simplifications. Policy not made here!

Personalized Medicine Stakeholders

- Regulatory
- Epi/EBR
- Health care providers
- Payors
- Academic/Gov't R&D
- Industry
- Patients
- Others

Medical Devices (Including IVDs)

Safety

- *There is reasonable assurance … that the probable benefits … outweigh any probable risks. [21CFR860.7(d)(1)]*

Effectiveness

- *There is reasonable assurance that … the use of the device … will provide clinically significant results. [21CFR860.7(e)(1)]*

Risk-Based Classification of IVDs

- **Class III: most complex, high risk**
  e.g. **cancer diagnosis or screening, drug selection**
    - *Premarket Application [PMA]*
    - *Safety, effectiveness*
- **Class II: more complex, moderate risk**
  e.g. **prognosis, monitoring in already diagnosed cancer patients**
    - *Premarket Notification [510(k)]*
    - *Substantial equivalence, special controls*
- **Class I: common, low risk devices**
    - *Most exempt from premarket submission*
    - *General controls*

IVD Regulation Aims

Clarity and reliability concerning:

- Test Description
- Intended Use
- Instructions for Use
- Performance Claims
- Manufacturing
- Problem Detection/Resolution

Performance Claims

- Analytical Validity
  - Sufficiently accurate and precise measurement of the analyte
- Clinical Validity
  - Biological/medical significance of the test result
- Clinical Utility
  - Impact on patient care and outcome

Challenges in Establishing Analytical Validity

- Reference methods and materials
- Analytical specifications for multivariate tests
- Clinical samples (number, kind, age/storage, spanning the range of analytical requirements)
- Full-spectrum assessment (pre-analytical, complete analytical process)

Challenges in Establishing Clinical Validity

- Sufficient number of patients/samples
  - Rare alleles, private variants/mutations
- Representative sampling of patients
  - Biased selection, subsets by design
- Diagnostic "truth"
  - "Soft" reference diagnosis, verification bias
- Follow-up/Outcome
  - Time/cost, endpoints

Omapro and T315I Testing

NDA 022-374
OMAPRO (omacetaxine mepesuccinate) for injection [ODAC, March 2010]

- Accrual using multiple independently developed laboratory tests
- Gaps, discordances with central labs' testing
- "**VOTE**: Should a well characterized *in vitro* diagnostic to identify patients with the T315I mutation be required and reviewed by the FDA and correlated to clinical trial results prior to approval of omacetaxine for the proposed indication?"
- RESULT: Yes=7, No=1, Abstain=0

New Drug, New Test (Indications)

Basel, 23 April 2010

Genentech submits supplemental application to FDA for Herceptin in advanced HER2-positive stomach cancer

http://www.roche.com/investors/ir_update/inv-update-2010-04-23.htm

Aug 11, 2009

Dako enters collaboration with Genentech on diagnostic tests for patients with stomach cancer

http://www.dako.com/us/index/aboutdako/newsevents/news/news_dako_enters_collaboration_with_genentech_on_diagnostic_tests.htm?setCountry=true&purl=index/aboutdako/newsevents/news/news_dako_enters_collaboration_with_genentech_on_diagnostic_tests.htm

Basel, 21 October 2010

FDA approves Herceptin for HER2-positive metastatic stomach cancer

First targeted medicine shown to improve overall survival in HER2-positive stomach and gastroesophageal junction cancers

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/103792s5250lbl.pdf

Progress for Analytical Validation

- Technical assessment and standards
  - MAQC, NIST, industry
- Analytical and clinical specifications coordinated during test design, verification, validation
  - Medical decision points
- Sample collection, storage, annotation
  - Gov't, industry, patient groups

Progress for Clinical Validation

- Clinical sample specification, acquisition, retention, maintenance, accessibility
- Well-matched (incremental?) intended use, evidence, and claims
- Coordination between therapeutic product and diagnostic device developers and reviewers
- Better study/trial designs

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