FDA's Role in the Regulation of In Vitro Diagnostic – the search for gold

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MEDICAL DEVICE AMENDMENTS OF 1976

General Controls

- Register and List
- Follow good manufacturing practices
- Report device failures

General Controls

- Inventory of tests on the market
- Tools to require good manufacturing practices
- System for remedying device failures

Premarket Review

- Division of Clinical Laboratory Devices (DCLC)
- 60 scientists

Classification System

- Risk/knowledge based
- Class II devices - put into place a quest for standards
- Standards working group formed (glucose and hemoglobin)
- Methodologies/materials sought
- Extensive learning process but no products

Submissions Reviewed

- Premarket Notification 510(k)s
- Premarket Approvals (PMAs)
- Both have performance and labeling requirements
- Accuracy/calibration

Submissions Reviewed

- Premarket Notification 510(k)s
- Premarket Approvals (PMAs)

Semantic Framework

- Old vs. New
- In vitro diagnostic devices

510(k)s

- ~ 500 submissions/year
- Substantially equivalent
- Comparisons to predicate device

510(k) Reviews

- Accuracy
- Precision
- Analytical sensitivity
- Analytical specificity

Limitations in Review

- Paper review
- Lack of performance standards

PMA Review

- ~ 6 - 12 applications/year
- Safety and Effectiveness

SAFE MEDICAL DEVICES ACT of 1990

- Broader scope to FDA's regulation
- Safety and effectiveness summary
- Safety and effectiveness statement

Clinical Performance Characteristics

- Clinical sensitivity
- Clinical specificity
- Predictive values

Limitations of Review

- Lack of “gold standards”
- Overt and latent bias
- Lack of performance standards

Labeling of in vitro diagnostic devices 809.10(b)

- Proprietary and established names
- Intended Use(s)
- Summary and explanation of test
- Principle of procedures

Labeling 809.10(b) (continued)

- Information on reagents
- Information on instruments
- Information on specimen collection and preparation

Labeling 809.10(b) (continued)

- Procedures
- Results
- Limitations of the procedure

Labeling 809.10(b) (continued)

- Expected values
- Specific performance characteristics
- Bibliography
- Name and place of business
- Date of the package insert

Intended Use

- Type of review
- Questions raised
- Data required

Scientific Model

- Literature
- Voluntary Standards
- FDA guidances

Development of a Scientific Model

- Upfront design of the study
- Careful and meticulous collection of data
- Sound interpretation of results

Quest for Standards

- Internal
- External
- Founding member of NCCLS
- Quick to support/adapt WHO and CDC methods and materials

Quest for Standards

- Methods standards
- Materials standards

Time Honored Informal Use

- Conformance to methods standards simplifies review
- Use of materials standards simplified review
- Examples are CDC cholesterol and HbA1C programs (utilize both) and use of WHO hCG materials which anchor submissions

Need for Standards Increased

- Quality system regulations
- Drive for international harmonization
- Changes in premarket program to allow formal use of standards

Possible to Recognize Standards

- Process outlined on internet
- Allows a declaration of conformity
- Reduce submission requirements
- Targeted toward methods; does not exclude materials

Abbreviated 510(K)

- Abbreviated
- Simplified
- Common grounds for clearance and labeling
- Rapid TAT

Abbreviated 510(k)

- Variable in dimensions
- Narrow and focused or comprehensive
- Partial or complete

Method Standards

- 53 NCCLS voluntary standards
- Growing number of FDA guidances
- ISO documents

Materials Standards

- Calibration
- Demonstrate accuracy/performance
- Calibration verification
- Quality Control
- Training
- Proficiency testing

FDA Review Process

- Benefit immensely from standards
- Needs standards
- Not standards driven
- We would like to change this culture; her 2

FDA Dual Mission

- Allow rapid access to good new technology
- Prevent bad products from being marketed
- Obvious inherent tension
- Standards can help

GOOD SCIENCE