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



◆ 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



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◆ Premarket Approvals (PMAs)



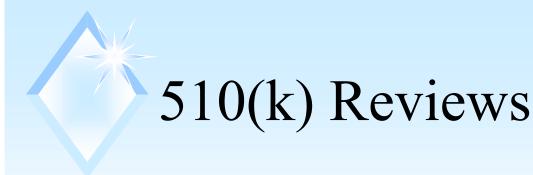
Semantic Framework

♦ Old vs. New

◆ In vitro diagnostic devices

510(k)s

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



- ◆ Accuracy
- **♦** Precision
- ◆ Analytical sensitivity
- ◆ Analytical specificity



Limitations in Review

◆ Paper review

◆ Lack of performance standards



PMA Review

 $\bullet \sim 6$ - 12 applications/year

◆ Safety and Effectiveness



SAFE MEDICAL DEVICES ACT of 1990

◆ Broader scope to FDA's regulation

◆ Safety and effectiveness <u>summary</u>

◆ Safety and effectiveness <u>statement</u>



Clinical Performance Characteristics

- ◆ Clinical sensitivity
- ◆ Clinical specificity
- ◆ Predictive values



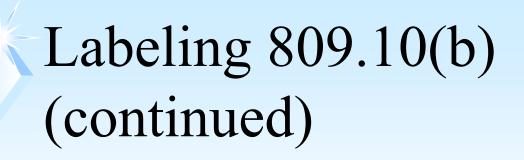
Limitations of Review

- ◆ 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



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



- **♦** 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



- ◆ 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



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



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



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

Materials Standards

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



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



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



GOOD SCIENCE