Mass Spectrometry in the Clinical Laboratory
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What’s so great about Mass Spec?

Analytical Sensitivity
Analytical Specificity (Selectivity)

Cost and Flexibility

What’s the downside?

"I think I may have spotted something!"
Throughput and Automation

Typical Systems

- LC-MS/MS system
  - Throughput of 10-20 specimens/hour
  - Not "one size fits all" for analytes
  - Samples preparation performed in batches

- Automated Clinical Chemistry Analyzer (Tox)
  - Throughput of 50-100 tests/hour (theoretical up to 600)
  - Multiple methods are available linked to test order
  - Random access testing – no batches needed
  - Parallel analysis

Lab Developed Tests

- FDA has determined that LDTs must be regulated at some level

- 2-day public hearing in 2010 for comment

- Risk-based review of LDTs

- Guidance has not been released yet
What does the FDA have to do with this?

What does the FDA have to do with this?

Enforcement Discretion

FDA Concerns

- Increasing number of LDTs
- Lack of clinician/pathologist/patient relationship
- Used as ‘market entry’ for newly developed tests
- Higher risk applications; less clinical validity
Concerns from Lab Industry

• Uneven playing field for IVD
• FDA review is slow
• Limit uptake of testing by ‘local’ labs
• Quality of tests

Concerns from Clinical Labs

• Limits availability of tests for patient care
• Limited resources to deal with FDA process
  – Most LDTs could be classified as high-risk
• Inconsistent evaluation of analytical and clinical validity
• Minimized role of laboratory director
  – Clinician-FDA-patient alternative

Proposed Guidance for LDTs

• CAP: joint system combining lab accreditation and regulatory review (risk-based)
Proposed Guidance for LDTs

- **CAP:** lab accreditation + regulatory review

- **FDA:** framework to encompass ALL LDTs and close regulatory gap
  - Some exemptions for ‘rare disease’ tests

- **Burgess Legislation:** introduced this year; removes FDA from the LDT loop
Burgess Legislation

• Oversight of LDTs by HHS rather than FDA
• Creates LDT test registry
• Data on analytical and clinical validity must be submitted for new LDT
• Lab must investigate adverse events linked to LDT results
• HHS can use accreditation organizations
• New program supported by fees assessed to labs performing LDTs

Harmonization of Methods

CAP Acceptability Criteria for TDM
Medical Decisions

- Tacrolimus
  - Therapeutic target published at 5-15 ng/mL (sometimes even 20)
  - Peer mean is not always ‘truth’
  - Actual targets are narrower and dependent on time relative to transplantation
How are these challenges being met?

Vendors

Guidance Documents
- Food and Drug Administration (FDA)
  - Guidance for Industry – Bioanalytical Method Validation
- Clinical Laboratory Standards Institute (CLSI)
  - C50, C57 (in development), C60 (in development)
- Scientific Working Group for Forensic Toxicology (SWGTOX)
- European Medicines Agency (EMA)
  - Guideline on Bioanalytical Method Validation
QUESTIONS??

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What’s in store for the next day or so?

• Discussion of CLSI C60 guideline in development
• Interactive session on LC-MS troubleshooting
• Discussion of tools available for method development and testing
• Updates on existing LC-MS applications
• Discussion of emerging applications for LC-MS