



Aspergillus *Assays*: Regulatory Issues

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Objectives

- Regulatory Background
- What we look for
 - Administrative/Regulatory
 - Summary
 - Studies
- What Sponsors should consider



Regulatory Background

- Federal Food, Drug, and Cosmetic Act of 1938 (The Act)
- Medical Device Amendments of May 28, 1976
– classified all existing IVDs
- Clinical Laboratory Improvement Act (CLIA) 1988
- Safe Medical Devices Act of 1990
- FDA Modernization Act (FDAMA) of 1997



Classification

- Class I Device
 - General Controls sufficient
 - Test result does not present unreasonable risk of injury
- Class II Device
 - Special Controls Needed
 - Erroneous Test result may present risk
- Class III
 - Test results present a risk of misdiagnosis
 - Valid scientific evidence required

Classification of Aspergillus

Assays



- 21 CFR Section 866.3040
- Aspergillus spp. serological reagents to identify antibodies to Aspergillus spp in serum
- Class I general controls. Exempt, Jan.14, 2000
- Limitations to exemptions



Limitations to the Exemption

- For measuring an analyte that serves as a surrogate marker for screening, diagnosis, or monitoring life-threatening diseases or to monitor therapy; (e.g. invasive aspergillosis)
- For identifying or inferring the identity of a microorganism directly from clinical material



Demonstrating Test Performance

- What is Intended Use?
- Who is target population, pediatric, adults, immunocompromised,
- What is being detected?
- What specimen matrix, plasma/serum, BAL, cultured isolates



Important Considerations

- Criteria used to define Aspergillosis
- Defining Performance yardsticks
- Comparator or Reference Method, i.e., culture, histology
- Appropriate specimen, timing, handling
- Disease spectrum and intra-species variation



Analytical Data

- Principle of the test
- How it is characterized
- How assay cutoffs are determined
- Any interferences
 - Endogenous: Lipids, Bilirubin, immunological
 - Exogenous: Anticoagulants, medications
- Any Cross-Reactivity
 - Other Viral or bacterial agents, or medical conditions related or unrelated; Mycoplasma, CMV, ANA, Rheumatoid factor



More Analytical

- Reproducibility: three levels, moderate and low positive, high negative
- Precision
- Limits of Detection of the Assay
- Specimen matrix, if different types are claimed



Clinical Study Requirements

- Support the Intended Use, i.e., indications and conditions for use.
- Probable benefit of the test results should outweigh any foreseeable misdiagnosis.
- Unified Multi-site Study Protocol
- Foreign Studies - Declaration of Helsinki



Clinical Studies

- Clinical Study Protocol
 - Inclusion & Exclusion Criteria
 - Patients with Probable IA, Proven IA, no Signs or Symptoms
 - Target Population Described using accepted criteria – e.g., IFICG, MSG, NIAID
 - Reference methods and/or predicate devices
 - Statistical methods described
 - Quality Control methods described



More Clinical Studies

- Sensitivity
 - Definition of “Truth” i.e., true positives
 - Diseased, how diagnosed
 - Population supports claims; transplant patients or hematologic malignancy
- Specificity
 - Definition of true negatives
 - Normal Healthy subjects
 - Patients with similar symptoms



Additional Considerations

- Submit pre-submission protocol for FDA review
- Plan Pre-submission meetings
- Be consistent across sites
- Clearly define patient groups
- Stratify data



Line Data

- Stratified by sites, different populations, various matrices
- Tables showing data results for predicate and new tests
- Clinical diagnosis and results of other diagnostic procedures



Summary

- Regulate products used to test human specimens to diagnose illness or health
- Product Classifications important but does not always drive review
- Standardized labeling and directions for use with supporting data important
- Appropriate Documentation of Data important to include with submission