Autoimmune Disease 510(k)s: Special Considerations

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Outline

- Background
- What's different about these tests?
- What does FDA look for during review?
  - Analytical
  - Clinical
  - Labeling
- Online Resources

Autoimmunity

- *When immune responses to self go bad…*
- T cells and B cells both play a role
  - Production of auto-antibodies against specific tissue components (enzymes, structural proteins, DNA, etc.)
- Mix of genetic and environmental factors
- More common than you think
  - 14 – 22 million (5 - 8%) in US, mostly women
- ~80 different diseases

Classifying Autoimmune Diseases

- Systemic
  - Rheumatoid Arthritis
  - Systemic Lupus Erythematosus
  - Sjogren's Syndrome
- Organ-specific
  - Type I Diabetes
  - Hashimoto's thyroiditis, Graves' Disease
  - Celiac Disease, Ulcerative Colitis

Testing for autoimmune diseases

- Relies on detection of autoantibodies as a marker of disease
- Typically used as an “aid in diagnosis in conjunction with other clinical findings”

How these Tests are Regulated

- Tests used as an 'aid in diagnosis' usually
  Class II
- 21 CFR §866 Subpart F – Immunological Test Systems
- Choosing a predicate

What's different about autoimmune tests?

- Very few reference standards to calibrate assays
  - Usually have to look at outcomes, not direct comparison of numerical result (2x2 tables)
  - Can't claim a test is quantitative
    - Semi-quantitative (report a number)
    - Qualitative (positive or negative)
- Trying to assess a polyclonal response
  - Very difficult to correlate severity with assay
- Not all patients with disease will have autoantibodies to your antigen
  - Ex: only ~ 70% SLE patients are dsDNA Ab +

Indications for Use

- Include:
  - Assay and company name
  - Technology
  - Instrument name/system (if applicable)
  - Sample matrices
  - Semi-quantitative or qualitative
  - Clinical use (aid in diagnosis of what?)
  - Setting (e.g. Rx use)

Analytical Performance Testing

- Precision or reproducibility
- Linearity, LoB, and LoD
- Assay cut-off (reference range)
- Analytical specificity
- Effect of interferents
- Controls & calibrators
- Stability: assay & sample
- Method comparison to existing predicate

Precision…

- Precision:
  - how close are repeated readings? (Semi-quantitative assays)
- Choose samples across assay range
  - Especially around clinical decision point
- Lots of repeats
  - CLSI EP5-A2: Evaluation of Precision in Quantitative Assays
- Assess With-in run, Between-Run/Days, Total, Between Lots

…and Reproducibility

- Reproducibility:
  - how often do you get the expected answer? (Qualitative assays)
- Focus on cut-off
  - Need samples ± 25% cut-off
- Lots of repeats
  - CLSI EP12-A: Evaluation of Reproducibility in Qualitative Assays

Linearity

- Not for qualitative assays
- Linearity: CLSI EP6-A
  - cover your claimed range
  - Use step-wise dilutions
  - Several samples a good idea

LoB, LoD and LoQ

- Not for qualitative assays
- Limit of Blank (LoB)
- Limit of Detection (LoD)
  - This will be lower limit of your assay range
- Limit of Quantitiation (LoQ) helpful
- Follow CLSI EP17-A

Assay Cut-off

- Essentially the point where negative -> positive
- Several methods to establish
  - +3SD mean of normal population
  - ROC analysis of negative and positive samples
  - Adjusting assay components to meet a specific number
- These samples cannot be used in method comparison or clinical comparison studies!
- Establishing correct cut-off is very important to assay success

Analytical Specificity aka Cross-reactivity

- Is your test specific for autoantibody or disease being tested for?
- Establish by testing samples from different, related, disease populations or samples of known specificity
  - Reference panels, consensus standards very helpful!
  - Some Exs

Effect of interferents

- Do other factors change test results?
- Endogenous:
  - Hemolysis, lipids, bilirubin, albumin, HAMA
- Exogenous: drugs, ‘short’ draws
- Should test at ≥ 3 analyte concentrations:
  - Negative but > LoD
  - Around cut-off
  - Low/moderate positive
- Choose interferent concentrations based on physiology
- CLSI EP7-A: Interference Testing

Sample Matrix Comparison

- Example: serum vs. plasma
- Samples across assay range
- Prefer that different matrices be drawn from patient directly
- Regression analysis and bias analysis
- CLSI EP14-A2: Evaluation of Matrix Effects

- **Calibrators and Controls**
  - Explain your traceability and validation procedure
  - State your acceptance criteria

- **Stability**
  - Assay – unopened (shelf-life), opened
  - Explain testing method, summarize results
  - Sample – fresh, processed, frozen

Method comparison

- Equivalent results as a previous assay?
- Aim for ≥100 samples, evenly divided
- Have samples across claimed assay range
  - Only samples between LoD and upper limit for semi-quants
  - Present as a 2x2 table
    - Can't directly compare numerical results
  - Calculate Agreement – positive and negative
    - Include 95% CIs
- Helpful: CLSI EP9-A2: Method comparison and bias estimation

Clinical comparison

- Does your test aid in diagnosis?
- Example: “your interesting disease” (YID)
- Evaluate samples from :
  - YID *but* with unknown antibody status
  - diseases related to YID
  - diseases in differential diagnosis of YID
- Evaluate in 2x2 table
  - Test result (+/-) versus YID diagnosis (+/-)
  - Calculate sensitivity and specificity, 95% CI

Method Comp vs. Clinical Study

- Often can use the same data set:

Method Comp	Clinical Study
Clinical Dx not critical	Clinical Dx crucial!
Only use samples w/in measuring range of both assays	Use all data
Samples should be distributed across measuring range	Sample distribution not critical
Need samples around the cut-off	Should have samples around cut-off

Presenting Results Example:

		Clinical Disease or Predicate Assay		
		Positive	**Negative**	***Total***
Your Assay	**Positive**	108	5	113
	Equivocal	2	4	6
	Negative	9	239	248
	Total	119	248	**367**

Regarding Equivocal as Negative:

Sensitivity: 90.8% 95% CI: 84.2 – 94.8%

Specificity: 98.0% 95% CI: 95.4 – 99.1%

Regarding Equivocal as Positive:

Sensitivity: 92.4% 95% CI: 86.2 – 96.0%

Specificity: 96.4% 95% CI: 93.2 – 98.1%

Equivocal Results

- Gray zone between negative and positive
- How to evaluate?
  - Calculate Method and Clinical comparisons twice:
    - Considering equivocal samples as negative
    - Considering equivocal samples as positive
  - Report both sets of analysis

Statistical Considerations

- Statistical Guidance for Reporting Diagnostic Tests

www.fda.gov/cdrh/osb/guidance/1620.html

Labeling

- Follow 21 CFR §809.10
- Keep summary relevant to your Intended Use
  - Don't stretch your claims
- Intended Use, Indications for Use, and 510(k) Summary must match exactly

Common Mistakes:

- No samples around assay cut-off
- Same samples used to validate cut-off re-used to establish method comparison and/or clinical performance
- Not covering claimed assay range (precision and linearity)
- Not choosing clinical samples that reflect intended use
- Using samples with known antibody status

Online Resources

- 510(k) database:
  - Search by 510 #, product code, device name, applicant name
  - Links to lots of useful dBs
  - Review templates after ~September 2003
  - http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm
- Device Advice
  - CDRH specific! Lots of great background on pre- and post-market stuff
  - http://www.fda.gov/cdrh/devadvice/
- CDRH Guidance Document database
  - For industry and FDA – what we look for or require for particular devices or topics
  - http://www.fda.gov/cdrh/guidance.html

Questions?

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Thank you!