Antigen/Antibody Detection Assays for Malaria

A CDRH Perspective

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OBJECTIVES

- Discuss Regulatory Background
- Types of information needed
- Requirements for clinical studies for IVD antigen/antibody detection assays

Regulatory Background

- Food, Drug, and Cosmetic Act, 1938
- Medical Device Amendment, 1976
  - Section 513 (a) (1)
- Safe Medical Devices Act, 1990
- FDA Modernization Act, 1997

Class I Devices

- General Controls - E.g. GMP's, Registration & Listing, record keeping
- Test result does not to support life or prevent impairment of health.
- Test result does not present unreasonable a risk of illness or injury.

Class II Devices

- General Controls are insufficient.
- Special Controls - E.g., Guidance documents, labeling regulations, (21 CFR 809.10), standards.

Class III Devices

- Test is critical in the diagnosis of disease.
- Test results presents a risk of misdiagnosis, which leads to illness or injury.
- Valid Scientific evidence is required - i.e., well controlled clinical trials.

Devices for Detection of Plasmodium Antigen or Antibody

- Test results are of substantial importance in diagnosis and treatment of a life-threatening illness.
- Currently, Class III devices requiring a PMA

QBC System...Not a Predicate

- 1982 QBC System was cleared for HCT, HGB, WBC, Granulocytes, Lymphocytes determination. This was a Class III Automated Differential Cell Counter device.
- 1989 QBC System was modified to add the QBC Malaria Tube. The QBT Malaria tube was cleared for qualitative detection of acridine orange stained parasites.

Type of Malaria Antigen Assays in Published Literature

- Monoclonal and Polyclonal antibodies raised against excretory/secretory antigens.
  - Pf 9, heat-stable antigen
  - Pf HRP-2 histidine - rich protein
  - IFA, IHA, ELISA
  - DNA Probes
- None approved by FDA

Non-Clinical Studies

What we require

A. Characterization of components, description of antigen, antibody, controls, etc.

B. Limits of Detection of the assay

C. Setting of Cutoff values

D. Reproducibility/Precision

Non-Clinical Studies

E. Cross Reactivity - with other Plasmodium spp, other parasitemias.

F. Interference - from endogenous and exogenous substances.

G. Stability - should also stress storage and shipping conditions.

Clinical Studies

- Must demonstrate safety and effectiveness
- 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

A. Clinical Sensitivity

1. Clearly defined populations (endemic, and non-endemic)
2. Clear description of disease status - how defined. (Gold Std: Thin & thick blood smears)
3. Clinical Protocol: description of all methodologies used, exclusion, inclusion criteria, quality control)

Clinical Studies

B. Clinical Specificity

The populations tested should include patients with microscopic or other evidence of Plasmodium spp. other than those detected by assay, other parasitemias, other conditions with similar symptoms.

Clinical Studies

C. <u>Validation of Cutoff Values</u>

1. Clinical studies: validate cutoff values are appropriate for the target population.
2. Should represent the spectrum of patients presenting with early or fulminant disease.

Clinical Studies

D. Statistical Analysis:

Studies should provide an adequate representation of cases, subtypes, co-infection (95% CI)

- FDA statisticians would comment on appropriate models.

For More Information:

- Submit a pre-IDE
- Contact us
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