

# Regulatory Considerations When Detection Methods are Used in Clinical Trials

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Considerations for Malaria Drug Development

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# Outline

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## Background

- In antimalarial clinical trials, the assessment of parasitological response to therapy is an integral part of efficacy determination.
- Blood smears are the gold standard for malaria diagnosis and are currently used for enrollment and monitoring treatment outcome
  - Does not distinguish recrudescence from reinfection
- Several rapid diagnostic tests to detect malaria parasites are available (WHO, 2011). The only FDA cleared malaria rapid diagnostic test is the Binax Now<sup>®</sup> Malaria test.
  - In clinical trials, it may be used to enrich for patients with *P. falciparum* malaria. Test results have to be confirmed by blood smears.
  - Clinically, it is used for diagnosis of patients suspected of having malaria.

## Using a Diagnostic Test in Antimalarial Drug Trials

- *In vitro* diagnostic devices are a subset of medical devices which are “**reagents, instruments, and systems** intended for use in the **diagnosis of disease or other conditions**, including a determination of the state of health, in order to cure, *mitigate, treat, or prevent disease or its sequelae*” .... for use in the collection, preparation, and examination of specimens from the human body (21 CFR 809.3)

## Using a Diagnostic Test in Antimalarial Drug Trials

- *In vitro* diagnostic devices are cleared by the FDA Center for Devices and Radiological Health (CDRH)
  - CDER works closely with CDRH when a non-cleared *in vitro* diagnostic test is used in clinical trials
- Clearance of a device by CDRH does not automatically render it suitable for use in registration trials
- Lack of submission to, and clearance by, CDRH of a device does not render it automatically unsuitable for use in clinical trials
- The context of use and risk to patients enrolled are important considerations

## Tests - Contexts of Use

- Controlled Human Malaria Infection (CHMI) trials:
  - Monitor parasitemia in healthy subjects
  - Measure treatment outcome
- Treatment trials:
  - Enrichment/Enrollment
  - Monitor parasitemia in patients and measure treatment outcome
  - To differentiate recrudescence versus reinfection

# ICH E8 Guidance on General Considerations for Clinical Trials

- The methods used to make the measurements of the endpoints, both subjective and objective, should be validated and meet appropriate standards for accuracy, precision, reproducibility, reliability, and responsiveness (sensitivity to change over time).

## Cleared versus non-cleared FDA tests

- **For FDA cleared tests:**
  - Package Insert. Additional information that is relevant to the context of use in clinical trials may be needed.
- **For non-FDA cleared tests:**
  - The performance characteristics of the test in the actual laboratory where testing is performed are needed for our assessment of the test
  - The extent of validation information will vary with the context of use
- **For All tests (FDA cleared and non-FDA cleared tests):**
  - The context of use and ability to rely on test results for the specific purpose of use is important.
  - In addition to the performance characteristics, the quality assurance procedures that are implemented in the laboratory where testing is performed are important.



## Tests - Contexts of Use

The presentations that follow will elaborate on the tests used in clinical trials within each context of use.

- Controlled Human Malaria Infection (CHMI) trials
  - Dr. Sean Murphy
- Treatment trials
  - Dr. David Saunders

## Conclusions

- Blood smears are currently the gold standard for malaria diagnosis.
- Currently, the only FDA cleared malaria rapid diagnostic test is the Binax NOW<sup>®</sup> Malaria Test.
- FDA is open to use of newer parasite detection methods in clinical trials.
- For FDA cleared tests, context of use will determine if additional information besides what is in the package insert is needed.
- For non-FDA cleared tests, performance characteristics within the laboratory where testing is performed are needed for our assessment.

## Discussion Points

New molecular tests for malaria parasite detection are evolving.

- Assays that are appropriate for use in CHMI studies
- Assays that can be used in antimalarial trials for purposes of enrollment and monitoring therapy in endemic areas
- Assays that can be used to differentiate recrudescence versus reinfection