

# FDA Perspective: Scientific and Regulatory Issues Related to Anti-malarial Drug Combinations

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for Malaria Drug Development

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# Outline

- Regulatory framework that pertains to the development of drugs in combination
- Challenge encountered with development of anti-malarial drugs in combination
- FDA Guidance document on co-development of drugs
- Study design options to assess the contribution of individual drugs to a combination regimen.

# Regulations regarding development of drugs - 1

- New Drug Application: Substantial evidence of effectiveness should be demonstrated for the drug or combinations of drugs in adequate and well-controlled clinical trials.
  - “substantial evidence” means “evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts...on the basis of which ...the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”  
Food Drug and Cosmetic Act 21 USC § 355(d)
  - Adequate and Well-Controlled Studies, 21CFR 314.126

# Regulations regarding development of drugs in combination - 2

- Fixed-Combination Prescription Drugs in Humans, “Combination Rule”(21 CFR 300.50):
  - Data are required to demonstrate that each component of a fixed-dose combination contributes a measurable advantage over the individual components
    - e.g., increased efficacy, reduced emergence of resistance, fewer or less severe adverse events, or a simplified treatment regimen.

# Challenge

How to demonstrate the contribution of the individual anti-malarial drugs to the combination?

- Preclinical studies
- Clinical studies

# Pre-Clinical Evaluations of Anti-malarial Drug Combinations

Pre-clinical evaluations may include:

- In vitro activity of the combination versus individual drugs against laboratory strains and clinical isolates
- Activity of the combination versus individual drugs in animal models

# Clinical Studies: How to assess the contribution of individual drugs to the anti-malarial combination?

- Controlled Human Malaria Infection (CHMI) study?
- A comparative clinical study with a factorial design in adults (semi-immune population) with uncomplicated falciparum malaria?
- Ethical considerations – potential for suboptimal efficacy and development of resistance

# FDA Guidances for Industry

- Co-development of Two or More Unmarketed Investigational Drugs for Use in Combination (2010)
  - Focus is co-development of two or more unapproved drugs.
  - Approved drug(s) with an unapproved drug(s)
- Malaria: Drug and Nonvaccine Biological Products for Treatment and Prophylaxis (2007)
  - Focused on clinical trial design issues unique to malaria
  - Requires update (withdrawn from FDA website)

# Clinical Study of Drug Combinations

- *Scenario: Each drug alone has activity and can be administered individually*
- **Factorial Design:**
  - Compare combination and drugs alone to SOC
    - (AB vs. A vs. B vs. SOC)
  - Add drugs to the standard of care
    - AB + SOC vs. A+SOC vs. B+SOC vs. placebo + SOC
  - Could we consider administering drug(s) for a short duration but long enough to establish proof of concept, (e.g., effect on malaria parasite clearance at early time point post-treatment)?
    - Semi-immune/uncomplicated falciparum malaria/safety of subjects/ rescue therapy

## Phase 3 Anti-malarial Trials

Phase 3 trials comparing the combination regimen to the standard of care regimen generally will be sufficient to establish effectiveness if findings from *in vivo* or *in vitro* models and/or clinical data adequately demonstrate the contribution of each component to the combination drug regimen.

# Applications of the “Combination Rule”

- Malaria:
  - Artemether/ lumefantrine, COARTEM®
- Hepatitis C
- Tuberculosis

# Application of “Combination Rule”: Artemether/lumefantrine, COARTEM®

Two factorial designed studies which evaluated artemether or lumefantrine alone and in combination (China):

- A double-blind, comparative trial of Coartem versus artemether versus lumefantrine tablets (1994)
- A partially blinded, comparative trial of Coartem versus lumefantrine tablets and capsules (1996)
  - *Ethical concerns about use of anti-malarial monotherapy*

## Application of “Combination Rule”: Hepatitis C

- Hepatitis C guidance: May show the contribution toward efficacy of a multiple direct-acting antiviral (DAA) combination regimen using *in vitro* and clinical data.
  - Cell culture data
    - showing that DAA combinations slow or prevent the emergence of resistance compared to single drugs
  - Clinical data (early phase 2)
    - Addition of a drug to a DAA combination improves sustained viral response or reduces emergence of resistance

## Application of “Combination Rule”: Tuberculosis

- Early Bactericidal Activity (EBA) Study
  - Evaluates individual drugs and combinations of drugs to evaluate microbiologic outcomes in patients at early time points (i.e., 7 to 14 days)
- Superiority Study: Investigational drug + optimized background regimen versus placebo + optimized background regimen, e.g., multi-drug resistant (MDR-TB).

## Discussion

Assessment of the contribution of individual drugs to an anti-malarial combination is challenging!

- *In Vitro* Studies
- Animal Models
- Clinical Studies