Draft Guidance for Industry: Human Immunodeficiency Virus: Developing Vaginal Microbicides for HIV Prevention

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This presentation outlines sections from the draft FDA guidance '*Human Immunodeficiency Virus: Developing Vaginal Microbicides for HIV Prevention*'

FDA Microbicide Guidance

- **The draft guidance was released on November 21, 2012**
- **The public comment period ends on February 21, 2013**
  - **Feedback can be submitted as written comments or electronically at** www.regulations.gov
- **When finalized, the guidance will represent FDA's current thinking for developing vaginal microbicides**

Overview

- **Phase 3 trial considerations**
- **Combination product development**
- **Risk-benefit considerations**

Phase 3 Trial Design Considerations(1)

- **Placebo controlled, double-blind design is appropriate for microbicide phase 3 trials**
  - **Endpoint-driven trials measuring incident HIV infections as the primary endpoint**
- **Large sample size usually is necessary to provide adequate power to detect a statistically significant effect on HIV seroincidence**
  - **Sample size determined by several factors including:**
    - **Anticipated effect of the investigational agent**
    - **Local HIV incidence**
    - **Contribution of other available prevention methods**
    - **Participant discontinuation rate, losses to follow-up, pregnancies**

Phase 3 Trial Design Considerations(2)

- **Trials should provide a background HIV prevention package consisting of behavioral risk-reduction counseling and promotion of condom use**
- **An approved oral PrEP agent can be offered in the trial as part of the background prevention package depending on**
  - **Oral PrEP acceptability as standard HIV prevention locally and implementation in regions where trials are conducted**
  - **Alternatively, trials can be designed to enroll subjects who refuse oral PrEP as a result of intolerance, side effects, or personal preference**
- **Acknowledge this is an evolving topic; public comments will be taken into consideration before finalizing the guidance**

Phase 3 Trial Design Considerations(3)

- **Longer duration trials preferable as expected to mimic real-world effects of the prevention product**
  - **Capture effects of adherence, fluctuations in high-risk sexual behavior, concurrent use of other prevention methods over time**

- **Provide longer duration safety data**
  - **At least 12 month follow-up for all participants, and**
  - **24 month follow-up data from at least 50% of participants, and**
  - **All participants should be followed until the last enrolled participant completes trial**

Comparator Arm Challenges

- **With an approved microbicide, demonstrating superiority to placebo may not be considered appropriate**

- **Comparing efficacy to the approved product is appropriate: demonstrating either superiority or non-inferiority to the approved agent**
  - **Are superiority trials feasible?**
    - **May require an even larger sample size than present-day trials**
  - **Challenges with designing noninferiority trials (next slide)**

Non-Inferiority (NI) Trial(1)

- **A NI trial "seeks to show that the difference in response between active control and the test drug is less than some pre-specified NI margin"**
- **Relies heavily on previously demonstrated effect of the active control**
- **NI margin calculation based on demonstrated effect of the control drug including confidence intervals around this effect**

Reference: FDA Draft Guidance for Industry Non-Inferiority Clinical Trials

Non-Inferiority Trial(2)

- **Challenges with NI trial design**
  - **Related to uncertainty of assay sensitivity of the active control agent**
  - **Defining a NI margin may be challenging in trial with oral emtricitabine/tenofovir as an active control**
    - **A wide range of effect was observed in iPrEx, Partners PrEP, and Fem-PrEP trials and effects were highly dependent on adherence**
  - **Similar issues may arise with a microbicide active control arm depending on the level of effectiveness**

- **Justifying the NI margin is essential; sponsors are encouraged to engage in discussions with the FDA in advance of initiating trials**

Strength of Evidence

- **Product approval should be supported by evidence from at least two independent trials, each convincing on it's own**
  - **Statistically significant, two-sided p value < 0.05**
- **Evidence from a single large trial may be acceptable**
  - **Statistically significant, two-sided p value < 0.001**
- **Other issues to consider**
  - **Strong internal consistency across subgroups and sites**
  - **Generalizability of trial results**

Combination Product Development

- **Development approach may vary depending on type of combination product**

- **General considerations for developing the following combinations**
  - **Microbicide-device combination**
  - **Combination product intended for multiple indications**

- **Types of information needed to justify the proposed combination include**
  - **Rationale supporting the proposed combination and dose**
  - **Animal toxicity data for each drug separately**
  - **Combination animal toxicity studies may be needed** [Reference: ICH Draft Guidance M3(R2)]

Risk-Benefit Assessment

- **Effectiveness trials should be powered to detect at least 33% reduction in HIV acquisition**
  - **We recognize that lower HIV reductions may be relevant to high HIV prevalence regions**

- **The overall risk-benefit assessment relies on the totality of data including**
  - **Percent reduction in HIV acquisition**
  - **Toxicity profile**
  - **Potential for behavioral disinhibition or condom migration**
  - **Rates of other STIs**
  - **Resistance development (for systemically absorbed antiretroviral drug product)**

Summary

- **This presentation has covered select sections from the FDA draft guidance for vaginal microbicides**
  - **Please refer to the guidance document for details and other related regulatory issues**

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  - **Feedback can be submitted as written comments or electronically at www.regulations.gov**

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