Draft Guidance for Industry: Human Immunodeficiency Virus: Developing Vaginal Microbicides for HIV Prevention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

- Nonclinical considerations
- Clinical considerations
  - Early phase development
  - Safety considerations
    - Safety data in specific populations: pregnancy, adolescents
  - Phase 3 trial considerations
  - Combination product development
- Risk-benefit considerations
Nonclinical Considerations

• Nonclinical Safety
  – Guidance outlines the types of animal toxicology studies needed to support microbicide development
    • Studies evaluating local and systemic toxicity in animals
    • Reproductive toxicology studies and carcinogenicity studies

• Virology
  – Studies focus on identifying the mechanism of action and
    • Quantifying antiviral activity and selection of resistant HIV
    • Microbicide effects on other sexually transmitted infections (STI) and STI assays
      • Effects on normal vaginal flora
  – Animal model data considered supportive, and not necessary for approval
Early Phase Clinical Considerations

• Objective of early phase clinical development is to provide sufficient data for preliminary safety, tolerability, acceptability, and pharmacokinetics to support rational drug development and choice of dose/doses to take forth into late-phase trials

• Initial safety of the investigational microbicide
  – Data from sexually active healthy women
  – Data from at least 100-200 subjects dosed for 3-6 months are needed to characterize preliminary safety

• Early trials should evaluate product acceptability
Pharmacokinetic (PK) considerations

• Evaluating local PK
  – Cervicovaginal fluid drug concentrations measured at different timepoints after dosing
  – Effect of menses and tampon use on drug concentration should be evaluated

• Evaluating extent of systemic absorption and PK
  – Informs about the potential for systemic adverse events, and possibly resistance development in case of antiretroviral-based microbicide
  – Relevant in deciding the need for typical clinical pharmacology studies i.e., systemic drug interaction studies, etc.
General Safety Considerations

• Safety assessments for local and systemic toxicity
  – Local toxicity evaluation: pelvic examination, visual inspection, colposcopy in at least 1 early phase trial, evaluation for effects on local pH and microflora
  – Systemic toxicity evaluation: monitoring for adverse events and laboratory abnormalities
  – Frequency of safety assessments: performed in the first month of dosing and at least once every 1-2 months in phase 3 trials

• Size of the safety database should be approximately 3000 subjects exposed to investigational microbicide for at least 12 months
  – Larger or smaller database may be needed depending on product safety profile
Safety in Special Populations: Pregnancy\(^{(1)}\)

- **Premise for obtaining safety data in pregnancy**
  - Recognition that an approved product may be used during pregnancy despite lack of safety data in this population
  - Ideal to obtain safety data methodically in a prospective clinical trial setting with careful monitoring of subjects
  - Both the woman and fetus may stand to benefit from a microbicide

- **Guidance outlines types of data necessary for deciding continued product use in trial participants who become pregnant**

- **The decision to dose during pregnancy will be made by the FDA on a case-by-case basis**
Safety in Special Populations: Pregnancy\(^{(2)}\)

- Decision to dose pregnant women will depend on the safety and PK profile of the product
  - Animal reproductive toxicity data
  - Genotoxicity data
  - Data from chronic toxicity studies supporting dosing duration
  - Systemic PK data in non-pregnant women

- Protocol will require additional safeguards to assure safety of the pregnant participant and fetus
  - Reconsent pregnant participants
  - Increased safety monitoring: more frequent visits, laboratory testing, fetal monitoring
  - Follow-up provisions for exposed mothers and infants
Safety in Special Populations: Adolescents

- Conducting trials in the adolescent population involves unique regulatory, ethical and consent considerations; discussed in detail in the guidance.

- We recommend collection of adolescent safety data before microbicide approval:
  - Recommend a two-stage approach with initial data collection in the older 16-18 year age group first.
  - Data can be collected in a separate adolescent trial or through limited adolescent enrollment in ongoing phase 3 trials.
Other Safety Considerations

• Safety data with rectal use
  – For semisolid microbicide products, rectal safety data should be available at the time of NDA submission
  – This guidance does not address development of rectal microbicides
  – Evaluation of rectal safety of a vaginal microbicide is necessary because:
    • Potential off-label use after approval
    • Products deemed as safe with vaginal use may not be safe when administered rectally
  – Rectal safety study design discussed in the guidance

• Safety in postmenopausal age group
  – Collecting safety data in postmenopausal women is strongly encouraged; obtained in a separate trial or limited enrollment in phase 3
Phase 3 Trial Design Considerations

- Placebo controlled, double-blind design is appropriate for microbicide phase 3 trials
  - Endpoint-driven trials measuring incident HIV infections as the primary endpoint
  - Safety endpoints

- 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

- Trials should provide a background HIV prevention package consisting of 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:
  - 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

- Longer duration trials are preferred 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
  - Require at a minimum 12 month follow-up for all participants, and
  - 24 month follow-up from at least 50% trial participants, and
  - All participants should be followed until the last enrolled participant completes trial
Considerations for Trial Design without Placebo

- With an approved microbicide product, demonstrating superiority to placebo, i.e., placebo-controlled trials, may not be considered appropriate.

- Comparing efficacy to the approved product is appropriate.

- However, challenges with designing comparative trials:
  - Superiority trials may not be feasible due to sample size considerations.
Considerations for Trial Design without Placebo (2)

• Challenges with noninferiority (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 the 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 essential and sponsors are encouraged to engage in discussions with the FDA in advance
Strength of Evidence

• **Product approval** should be supported by evidence from at least two independent trials, each convincing on its 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**
  – Internal consistency across subgroups and different sites
  – Generalizability of trial findings
Combination Product Development

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

• Information necessary to justify the proposed combination
  – Rationale supporting the proposed combination and dose
  – Animal toxicity data for separate drugs
  – Drug-drug interaction data, if applicable

• Development approach may vary depending on the type of combination product
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
  – Resistance development for systemically absorbed antiretroviral drug product
  – Rates of other STIs
Other Issues to Consider

- Acceptance of foreign trial data
  - Microbicide trials are generally conducted outside the US in areas with relatively high HIV incidence
  - FDA regulations permit accepting foreign trial data provided the following requirements are met
    - Foreign studies meet the requirements applicable to US studies conducted under an investigational new drug application (21 CFR part 312), and
    - Clinical development program includes sufficient number of US subjects to ensure relevance of data to the US population
Summary

• This presentation has covered sections from the FDA draft guidance for developing vaginal microbicides for preventing HIV acquisition

• 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
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