# Guidance for Industry

# Vaginal Microbicides: Development for the Prevention of HIV Infection

**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Drug Evaluation and Research (CDER)**

**November 2014**
**Clinical/Antimicrobial**

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# Vaginal Microbicides: Development for the Prevention of HIV Infection

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## TABLE OF CONTENTS

*Contains Nonbinding Recommendations*

# Guidance for Industry[1] Vaginal Microbicides: Development for the Prevention of HIV Infection

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## I. INTRODUCTION

This guidance provides recommendations for the development of vaginal microbicides regulated within the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) for the prevention of human immunodeficiency virus (HIV) infection. Specifically, this guidance addresses the FDA's current thinking regarding the overall development program and clinical trial designs to support the development of vaginal microbicide drug products.[2]

Information in this guidance is also generally relevant for developing vaginal microbicides that are part of a drug-device combination product. Guidance on development and testing of devices can be obtained from the Center for Devices and Radiological Health (CDRH).[3]

For the purposes of this guidance, we define vaginal microbicides as intravaginal drug products that reduce the risk of HIV acquisition. Vaginal microbicides are designed to be self-administered products. Microbicides can be developed as vaginal formulations including gels,

[1] This guidance has been prepared by the Division of Antiviral Products in the Center for Drug Evaluation and Research (CDER) in cooperation with the Division of Bone, Reproductive, and Urologic Products in CDER at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biological products unless otherwise specified.

[3] See the guidance for industry *Latex Condoms for Men — Information for 510(k) Premarket Notifications: Use of Consensus Standards for Abbreviated Submissions* and the Class II special controls guidance document *Labeling for Natural Rubber Latex Condoms Classified Under 21 CFR 884.5300*. We update guidances periodically. To make sure you have the most recent versions of these guidances, check the FDA Medical Devices guidance Web page at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

creams, tablets, films, drug-impregnated sponges, and drug-impregnated vaginal rings. Microbicides therefore offer a women-initiated HIV prevention method, which would form a useful addition to the existing prevention interventions. Sponsors can choose to develop drug products with coitally dependent dosing (pre-coital dosing, or post-coital dosing, or pre-coital plus post-coital dosing) or a coitally independent dosing scheme (e.g., daily dosing, intermittent dosing, or sustained release formulation such as vaginal ring).

This guidance does not address other forms of HIV prevention such as prophylactic vaccination or prevention mediated exclusively by mechanical barrier devices (e.g., male condoms). Inquiries regarding vaccines should be addressed to the Center for Biologics Evaluation and Research. Inquiries regarding mechanical barrier devices should be addressed to CDRH. Prevention of sexually transmitted infections (STI) other than HIV also is not addressed in this guidance. Additionally, general issues of statistical analyses or clinical trial design are not addressed in this guidance. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[4]

Sponsors considering development of vaginal microbicides are encouraged to consult this guidance and to communicate with the FDA through the pre-investigational new drug application consultation program and throughout drug development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

## II. BACKGROUND

The natural history of HIV infection includes a brief symptomatic period characterized by intense viral replication or acute HIV infection. This acute phase is followed by a clinically latent period and eventual progression to a state of profound immunodeficiency known as acquired immunodeficiency syndrome (AIDS).

Sexual transmission accounts for the majority of HIV infections both in the United States and globally. Behavior change through counseling, male and female condoms, antiretroviral therapy for the infected partner, and treatment of STIs can reduce the risk of HIV acquisition. However, despite these prevention methods, HIV incidence in the United States has not declined and remains stable at 56,300 new infections annually (Hall, Song, et al. 2008). Worldwide, the annual incidence is estimated to be about 2.7 million infections (UNAIDS 2011).

[4] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In 2012 the first drug product for oral pre-exposure prophylaxis (PrEP), tenofovir/emtricitabine, was approved to reduce the risk of sexually acquired HIV infection in adults at high risk. Data from trials in both men who have sex with men and heterosexual populations supported this approval. Despite its efficacy, this intervention poses several challenges including adherence to daily pill intake, the potential for renal and bone toxicities, the potential for decreased condom use, and the development of resistance to drugs that are also used for HIV treatment.

With respect to women and the HIV epidemic, present trends indicate that women account for 23 percent of new infections in the United States (CDC 2010) and 50 percent of all new infections globally. Heterosexual transmission plays a major role in HIV infection in women, and among the available options for reducing heterosexual male-to-female transmission, virtually all require male partner agreement to be effective. For example, using male condoms, which are widely available through condom promotion programs, depends on the male partner's level of condom acceptance (Kulczycki, Kim, et al. 2004). In many settings, women are unable to insist on or negotiate use of condoms or another available prevention method. In these situations, gender inequality, reliance on men for economic security, and compromised relationship dynamics may contribute to the prevention challenge (Aziz and Smith 2011). Taken together, these limitations emphasize the need for novel prevention approaches that allow women to independently control their HIV acquisition risk. Lastly, a woman's product preference may change over time depending on factors including the desire to conceive, partner's product preference, perceived risk for other STIs, or dosing convenience. At-risk women need multiple prevention options to meet their needs. In this context, vaginal microbicides offer the potential of a unique female-controlled method.

## III. DEVELOPMENT PROGRAM

### A. General Considerations

#### *1. Nonclinical Considerations*

##### a. Nonclinical safety

General recommendations for supportive nonclinical safety studies including their design and timing are addressed in other FDA and ICH guidances for industry, such as the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals: Questions and Answers*. For a drug product currently approved as a vaginal formulation for another indication, additional toxicology studies usually are not needed unless the approved vaginal drug product is reformulated. Recommendations for biologically derived products are discussed in the ICH guidance for industry *S6(R1) Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals.* Nonclinical considerations specific to vaginal microbicide development are discussed in this guidance.

Sponsors should assess a candidate vaginal microbicide for the potential to cause cervicovaginal inflammation or epithelial breakdown. Local safety and tolerability can be evaluated alone or as

part of repeat-dose toxicology studies. These studies should include scoring systems to quantify the extent of erythema, edema, leukocyte infiltration, and ulceration or disruption of epithelium, as well as detailed histopathologic assessments of vaginal tissue. A positive control such as 4 percent nonoxynol-9 should be included for comparison. For drug products containing an entity originally approved as a nonvaginal formulation, sponsors should conduct bridging toxicology and vaginal irritation studies.

Sponsors should evaluate systemic drug absorption following vaginal administration because the extent of plasma exposures is a key determinant of systemic toxicity. When lower systemic exposures are achieved following vaginal administration in animals compared to humans, nonclinical studies using an alternate route of administration may be needed to attain the appropriate exposure. In addition to cervicovaginal and systemic toxicity, sponsors should assess local tolerance via rectal application in animal studies before evaluating rectal safety in humans.

Reproductive toxicology studies should be completed and submitted for FDA review before dosing pregnant participants in clinical trials (also see section III.A.5.c., Safety in specific populations (Pregnant women)). Sponsors should measure systemic drug exposures in these studies. Similar to repeat-dose toxicology studies discussed previously, if animal exposures are lower than human exposures, then sponsors should conduct animal studies with other routes of administration to yield relevant systemic exposures. In circumstances where systemic drug exposures in both humans and animals are below limits of detection, sponsors should conduct an embryo/fetal development study with vaginal drug administration to evaluate potential effects mediated through local and/or regional drug distribution.

Sponsors should conduct carcinogenicity studies in rats and mice, including one study with vaginal drug administration to evaluate for local tumorigenic potential. For detailed information for animal carcinogenicity studies, sponsors should refer to the ICH guidances for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals*, *S1B Testing for Carcinogenicity of Pharmaceuticals*, and *S1C(R2) Dose Selection for Carcinogenicity Studies*. The oral carcinogenicity studies may not be needed if systemic drug exposures in both animals and humans are below the limits of detection. In addition, the local carcinogenicity study may not be needed for drug products with systemic exposures below the limits of detection and with adequate clinical data supporting absence of vaginal irritation with long-term use. Sponsors are strongly encouraged to propose their plans for nonclinical carcinogenicity assessments during phase 2 of development to allow sufficient time for study conduct and completion in advance of a new drug application (NDA) submission. If sponsors determine these studies are not needed for their drug product, they should initiate discussions in phase 2 to seek FDA concurrence.

b. Nonclinical virology

The biology of HIV vaginal transmission is not fully understood and the following recommendations may be modified as the field evolves. In addition to identifying the mechanism of action, nonclinical virology studies should address the following:

- Quantification of antiviral activity and the potential for cellular toxicity
- Selection and characterization of resistant HIV
- Effects on other sexually transmitted pathogens and the assays used to detect them
- Effects on normal vaginal microflora

Validated animal models for predicting efficacy in humans do not exist. Sponsors often use animal models to obtain supportive activity data; however, they are not needed to support approval of an indication. Generally, animal model studies are designed to show a protective effect against vaginal challenge with simian immunodeficiency virus or chimeric simian/human immunodeficiency virus in nonhuman primates. While animal models can be useful for providing proof of concept of antiviral activity and for informing drug product development decisions, at present these models lack sufficient validation to support regulatory approval. Humanized mouse models also may be useful in evaluating activity against vaginal challenge of HIV; however, the limited availability of human hematopoietic progenitor cells may restrict the use of these models (Denton, Estes, et al. 2008; Berges, Akkina, et al. 2008).

**Quantification of antiviral activity and cellular toxicity**

Because the principal objective of the microbicide is to prevent HIV transmission, studies should demonstrate inhibition of HIV replication in cell culture. Dose-response curves should be generated to determine the range of antiviral activity. These results should reflect the concentration of the drug required to reduce HIV replication by 50 percent (i.e., 50 percent effective concentration ($EC_{50}$) value).

Sponsors should use well-characterized laboratory strains of HIV-1 in initial evaluations to validate antiviral activity. After demonstrating antiviral activity against standard laboratory strains, evaluation should be expanded to cover a broad range of clinically relevant viruses including those isolated from the reproductive tract, multiple isolates representing each of the HIV-1 clades, CCR5 and dual CCR5/CXCR4 co-receptor tropic strains, and HIV-2. The candidate microbicide should also have demonstrable antiviral activity against several (greater than or equal to 20) temporally and geographically distinct isolates, including U.S. strains and strains endemic to regions where clinical trials will be conducted. Additionally, sponsors should assess antiviral activity against multiple isolates from each HIV-1 clade and HIV-2. The median and range of $EC_{50}$ values should be provided.

Sponsors should assess antiviral activity in peripheral blood mononuclear cells, primary macrophage and dendritic cell cultures, and cervicovaginal explants because these cultures represent the cell types likely involved in sexual transmission of HIV (Wu and Kewalramani 2006). Assays including continuous cell lines such as ME-180 cervical epithelial cells (CD4-transformed cell line) or GHOST X4/R5 human osteosarcoma cells may provide supporting data; however, these cannot be substituted for primary cultures because their biological relevance to human infection is unclear at this time. Primary cultures should be harvested from several different donors to verify antiviral activity across a genetically diverse population of subjects. These studies are particularly important for drugs targeting host proteins (e.g., CCR5 or CD4) because polymorphisms may affect antiviral activity.

In addition to the diversity of viral variants and cellular targets, other variables associated with transmission may affect activity. Sponsors should perform assays under conditions consistent with drug product use to determine:

- Antiviral activity across a range of multiplicities of infections
- Antiviral activity following pH transition from an approximate pH 4 to pH 7
- Protection against infection by cell-free and cell-associated HIV-1 virus
- Antiviral activity in the presence of seminal plasma and cervicovaginal lavage fluid
- Virucidal kinetics (in seconds or minutes) for nonspecific agents inactivating virus

Furthermore, sponsors should verify antiviral activity of the proposed microbicide formulation to identify excipient effects. The results for the effect of each variable should include the fold-shift in $EC_{50}$ value relative to infection under standard conditions.

Studies determining range of antiviral activity should be conducted under biologically relevant conditions and results should demonstrate that antiviral activity is not a result of damage to host cells. Cytotoxic compounds may reduce capacity of the host cell to support HIV replication that may be misinterpreted as direct antiviral activity. To differentiate direct antiviral activity from negative effects on the host cell, cytotoxicity should be quantified as the cytotoxicity concentration ($CC_{50}$) value, the drug concentration required to reduce culture metabolism or viability by 50 percent.

Additionally, the therapeutic index (TI) should be calculated as the ratio of the $CC_{50}$ and $EC_{50}$ values ($TI = CC_{50}/EC_{50}$). Generally, a higher TI value indicates a more specific antiviral effect and greater likelihood that an effective concentration of the drug can be achieved without undesired off-target effects on the host cell. Further, the TI can be useful in comparing different candidate microbicides or in quantifying relative activity of a particular microbicide against different viral variants or different cell types. In general, we do not recommend development of a drug with a TI less than or equal to 10; sponsors interested in pursuing development of a drug with TI less than or equal to 10 should discuss the basis for pursuing development with the FDA. Sponsors should refer to the National Institute of Allergy and Infectious Diseases/Division of Acquired Immunodeficiency Syndrome (DAIDS)/National Institutes of Health nonclinical resources for assistance in developing their microbicide.[5]

**Selection and characterization of resistant virus**

HIV seroconversion during microbicide use may result in resistant virus and affect HIV treatment options. Understanding the pathway to resistance development (i.e., the amino acid substitutions that confer reduced susceptibility to an antiviral drug) is useful in understanding the potential risks of microbicide failure and in guiding resistance monitoring plans in clinical trials. Characterization of resistant isolates also can provide supporting evidence for the proposed mechanism of action.

[5] See http://www.niaid.nih.gov/labsandresources/resources/atrg/pages/microbicidesprevhivtrans.aspx.

Because the genetic barrier to resistance may vary as a function of drug concentration, resistant variants should be selected in cell-culture at different microbicide concentrations. Several independent resistant isolates should undergo genotypic and phenotypic testing. Resistance-associated substitutions should be verified by phenotypic characterization of site-directed recombinant viruses expressing the mutant protein. If substitutions arise in viral proteins or protein complexes targeted by approved antiretroviral drugs, cross-resistance should be assessed including:

- Assessment of the susceptibility of approved drugs to microbicide-resistant variants
- Assessment of susceptibility of the microbicide to variants resistant to approved antiretroviral drugs

**Effect on STIs and normal human microflora**

Local pathologic changes associated with STIs as well as vaginal microflora alterations may affect the risk for vaginal HIV transmission. Sponsors should test for antimicrobial activity against common STI pathogens, such as *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, herpes simplex virus type-2, and trichomonas. Testing antimicrobial activity is of particular importance for drug products with a nonspecific mechanism of action and/or a low TI. Testing also should be performed to assess static and cidal activity on normal resident microflora such as *Lactobacilli*. Sponsors should be aware that the microbicide may contain components inhibitory to STI assays (e.g., sulfated polysaccharides can affect certain polymerase chain reaction assays) that may interfere with STI diagnosis. Hence, microbicide effects on sensitivity of STI diagnostic assays used in clinical trials should be evaluated using concentrations consistent with drug product use.

c. Other nonclinical studies

Condom compatibility studies are nonclinical studies intended to evaluate effects of a microbicide on the physical properties of condoms. Concomitant use of microbicide and condoms is expected both in clinical trials as well as real-world use following microbicide approval, regardless of whether the microbicide is labeled for use with the condom. Condom compatibility studies are needed to determine whether use of microbicide with condoms affects the rate of condom failure compared to condoms used alone.

Sponsors should refer to the American Society for Testing and Materials (ASTM) D7661-10, Standard Test Method for Determining Compatibility of Personal Lubricants With Natural Rubber Latex Condoms, for study design and methodology. Studies should include both male and female condoms composed of a variety of materials including natural rubber latex, polyisoprene, polyurethane, and nitrile. In addition to baseline, conditioned, and positive controls, concurrent evaluation of the effects of microbicide and placebo on each condom type should be performed. Data analyses and presentation should follow recommendations outlined in the above-mentioned ASTM standard.

In addition to condom compatibility testing, sponsors should perform viral penetration testing to assess the drug's effects on the barrier properties of male and female condoms. Sponsors should

use the method described by Lytle et al. (1992) to evaluate viral penetration. Sponsors are strongly encouraged to provide study proposals for FDA review and comment before initiating nonclinical compatibility studies.

Positive or equivocal findings in nonclinical compatibility studies may prompt the need for clinical data to fully understand effects of microbicide on condom function. Clinical data obtained from condom function studies are discussed further in section III.C.4., Condom Device/Function Studies.

Sponsors should also evaluate the effect of a microbicide on the physical properties of other commonly used barrier contraceptive devices (e.g., diaphragms). Before initiating these studies, sponsors should contact the FDA to obtain feedback for their proposed plan and/or protocol.

*2. Drug Development Population*

Clinical development should be pursued in women at risk of acquiring HIV through sexual transmission. Microbicide efficacy trials generally are conducted in high HIV prevalence areas or populations because the HIV seroconversion rate is a critical factor in determining sample size. Because the largest number of new HIV infections occurs outside the United States, clinical efficacy data supporting an indication likely will be obtained from trials conducted at foreign sites. FDA regulations permit accepting foreign trial data in support of a marketing application, provided the foreign studies meet the same requirements in 21 CFR part 312 as are applicable to U.S. studies conducted under an investigational new drug application.[6] The clinical development program should include U.S. subjects to ensure applicability of data to the U.S. population. Additionally, for certain vaginal formulations, data from a label comprehension study conducted in U.S. subjects should be submitted with the NDA (see section III.C.5., Labeling Considerations).

*3. Early Phase Clinical Considerations*

Because HIV seroconversion is an infrequent event even in high prevalence areas, proof of concept can be measured only in trials with relatively large sample sizes. As a result, vaginal microbicide development generally proceeds directly from phase 1 to large-scale phase 2b or phase 3 trials. The 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 or doses to take forth into late-phase trials.

a. Safety and pharmacokinetic considerations

Initial safety should be evaluated in sexually active healthy women at low risk for potential confounders for evaluating safety/tolerability, such as STIs or baseline cervicovaginal abnormalities. Safety evaluations should focus on local toxicities of the cervicovaginal area and the female reproductive tract, as well as systemic toxicities. Initial studies can obtain data reflecting regular drug product use for at least one complete ovulatory/menstrual cycle. Studies

[6] See the guidance for industry *Acceptance of Foreign Clinical Studies*.

of at least 3 to 6 months dosing duration are needed to identify toxicities from cumulative drug product use. Generally, data from at least 100 to 200 subjects are needed to characterize the preliminary safety profile.

Systemic absorption should be determined early in drug development because of important safety and drug development implications. For systemically absorbed drug products, the potential for systemic adverse events should be monitored from early trials onward. Knowledge about systemic absorption influences the type of clinical pharmacology studies needed for drug product development. For example, typical clinical pharmacology studies (e.g., drug interaction, hepatic impairment, renal impairment) may not be needed if systemic exposure is low or undetectable. For drug products containing either a drug originally approved for HIV treatment or a new molecular entity in the same class as an approved drug for HIV treatment, the presence of sub-inhibitory but detectable systemic drug concentrations can potentially result in resistance or cross-resistance, respectively, in the event of HIV seroconversion.

Local pharmacokinetic (PK) evaluations should include serial assessment of cervicovaginal fluid concentrations at different time points after dosing to estimate the level of local exposure as well as to determine elimination of the drug locally. Local drug distribution can be quantified by collection of cervicovaginal fluid samples from multiple regions of the vaginal lumen. Researchers have used magnetic resonance imaging and other imaging techniques as another mechanism to determine local and regional drug distribution. Hypothetically, to be optimally effective, a vaginal microbicide should uniformly coat the entire vaginal lumen and cervix. However, there is presently no clear evidence linking extent of local coverage or tissue distribution or local drug exposure to clinical outcome for vaginal microbicides. Tissue samples obtained by biopsy can be used to quantify the extent to which the drug is taken up by cervicovaginal epithelium. In addition, local PK data collected in early studies should include an assessment of microbicide drug concentrations during menses, both with and without tampon use. For vaginal ring microbicides, sponsors should determine local tissue drug concentrations at different time points after ring removal to provide an estimate of the elimination of the drug locally following ring expulsion or loss.

b. Drug product characteristics that affect end-user acceptability

Trials should assess drug product characteristics that are expected to affect user acceptability early in drug development. Although phase 1 acceptability data may not reflect phase 3 or postmarketing acceptability, early data can guide drug product reformulation needed to optimize acceptability before embarking on large scale trials. Poor or low acceptability may be secondary to unfavorable physical attributes (e.g., viscosity, odor, color, taste). For semisolid gel formulations, vaginal retention should be assessed because excessive vaginal leakage after application may be undesirable and also lead to poor distribution and possibly compromised drug effect.

c. Dose selection

Dose selection poses a unique challenge to microbicide development. The ability to use PK/pharmacodynamic (PD) models for dose selection is contingent upon establishing

measurable and valid PD endpoints. Therefore, typical dose-response or exposure-response analyses are unlikely to be helpful for microbicides unless validated surrogate markers of protection are identified. In vitro antiviral activity data combined with local exposure data (e.g., vaginal and cervical concentrations) can be used to predict a minimally efficacious dose. Protein-binding of the drug product in vaginal fluid also should be taken into consideration for highly protein-bound drug products when selecting doses. Additionally, animal toxicity findings and safety findings in phase 1 clinical trials can provide further information guiding human dose selection. Another consideration is systemic absorption; in some instances higher doses may not be preferred because of increased systemic absorption and a greater likelihood of systemic adverse events.

*4. Efficacy Considerations*

Despite advances in the HIV and microbicide field, there are several challenges in the clinical development of vaginal microbicides. Some challenges in evaluating clinical efficacy are addressed below.

In addition to biological efficacy, variables such as drug product adherence, concurrent use of other prevention methods (e.g., condoms, oral PrEP), and frequency of high-risk sexual behavior are closely linked to the overall effectiveness of a vaginal microbicide. Because usage rates of microbicide and/or other prevention methods as well as sexual behavior patterns are expected to fluctuate over time, and long-term safety events (e.g., epithelial disruptions) may potentially reduce efficacy over time, longer duration efficacy trials are preferred because they can capture the effect of these variables and are more likely to reflect the real-world effects (Lagakos and Gale 2008).

Efficacy trials should measure the rate of new HIV infections. Given the relatively low incidence of seroconversion even in high-prevalence populations, a large sample size usually is necessary to provide adequate power to detect a statistically significant effect on HIV seroincidence. As with other drug trials, sample size calculations should account for the anticipated effect size of the drug product, as well as loss to follow-up and dropouts caused by adverse events. An additional consideration is the anticipated pregnancy rate, because pregnant women in microbicide trials should be taken off the drug product unless specific criteria are met (see section III.A.5.c., Safety in specific populations (Pregnant women)).

Risk-reduction counseling and promoting condom use are ethical imperatives during the conduct of microbicide trials. Additionally, an approved oral PrEP agent can be offered in the trial as part of the background prevention package. Offering oral PrEP depends on several considerations including 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. Importantly, condom promotion and other prevention interventions are likely to reduce the infection rate in the trial and further increase the trial sample size.

Accelerated approval (21 CFR part 314, subpart H), based on a surrogate endpoint considered reasonably likely to predict clinical benefit for a serious or life-threatening disease, is not

applicable for an HIV prevention indication. The endpoint of HIV infection, although a laboratory measurement, is considered to be reliably predictive of progressive clinical disease. At this time, other surrogates that are predictive of laboratory infection of HIV have not been defined. The assay used to diagnose HIV infection should be the most reliable assay available at the time of the trial.

Sponsors can request that the FDA expedite drug product development through mechanisms such as priority review and fast track designation.[7] The fast track designation allows for frequent interactions with the FDA and permits rolling review when an NDA is submitted. Proposals for fast track designation can be considered at any time during development depending on appropriate fulfillment of the designated criteria.[8]

*5. Safety Considerations*

a. Adequacy of the safety database

Microbicide efficacy trials will have a large sample size; therefore, it is anticipated the safety database will consist of several thousand subjects exposed to the proposed to-be-marketed dose for at least 12 months. A proportion of phase 3 subjects should be followed for a longer duration as outlined in section III.B.5., Trial Duration. Data from more subjects may be needed if safety concerns are identified during development. Alternatively, a smaller safety database may be considered adequate if the drug product is already approved for use by another route/formulation or is unapproved but has been evaluated substantially using other routes of administration. Sponsors are strongly encouraged to discuss their proposed safety database with the FDA at an end-of-phase 2 meeting or earlier.

b. General safety considerations

Local vaginal and cervical safety is a critical consideration for a vaginal microbicide. Sponsors should assess local toxicity through symptoms and signs for genitourinary and reproductive adverse events and by pelvic examination. Evaluations should focus on symptoms and signs representing genital irritation, inflammation, or mucosal breakdown. Pelvic examination should include visual inspection and speculum examination. Comparative safety data from randomized, double-blind trials using an appropriate placebo control are preferred to allow clear interpretation of safety findings. Severity grading of cervicovaginal abnormalities should be based on accepted grading criteria for genital toxicity such as the National Institutes of Health DAIDS genital toxicity table.[9]

[7] See http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies.

[8] See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics*.

[9] See http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx.

Colposcopy should be performed in at least one phase 1 trial following multiple drug exposures in sexually active women conducted early in drug product development. This technique was originally developed to detect local malignancy; specifically for microbicide trials, the examination should focus on findings reflecting potential drug toxicities including epithelial disruption. Sponsors should refer to standard criteria for colposcopy technique and training for vaginal microbicides.[10] Depending on the safety profile and colposcopic findings in phase 1, we will determine the need for colposcopy in subsequent phase trials. We do not consider vaginal biopsies necessary unless indicated by local toxicity findings. Trials should also monitor for adverse events reflecting drug effects on the uterus, fallopian tubes, and ovaries that may arise from regional drug distribution.

Sponsors should perform assessments for microbicide effects on vaginal pH, balance of vaginal microflora, and the frequency of other STIs. Significant shifts in local microflora may have clinical implications because the normal vaginal microflora is thought to play a role in preventing HIV-1 infection and other STIs (Myer, Kuhn, et al. 2005). Certain types of microflora imbalance or decreases in particular flora species can also increase the likelihood of bacterial vaginosis, urinary tract infections including urosepsis, and pelvic infections.

Systemic adverse reactions may arise if a drug product is systemically absorbed following vaginal administration. At a minimum, sponsors should evaluate systemic safety through adverse event assessment and routine laboratory tests such as hematology and chemistry parameters. The need for additional evaluation depends on the level of systemic absorption and expected or known risks of the drug product as indicated by nonclinical findings or toxicities observed in earlier human trials. For a microbicide originally approved as an oral formulation, sponsors should consider the established safety profile when forming a targeted safety assessment plan for trial protocols. For example, if thyroid function abnormality is a recognized toxicity with the oral formulation, appropriate laboratory testing of thyroid function should be included if significant systemic absorption is expected. Grading of nongenital adverse events and laboratory abnormalities should follow commonly used and accepted toxicity grading schemes.

For drug products intended for vaginal retention for a specified time period (e.g., a 28-day intravaginal ring), sponsors should collect safety data reflecting greater than the prescribed duration of exposure to characterize safety in case of drug product overuse.

Safety evaluations in phase 1 trials generally can be performed at weekly intervals or less frequently. In late-stage trials, sponsors should perform evaluations within the first month of starting the drug product and then at least once every 1 to 3 months. The protocol should have provisions to contact subjects or allow unscheduled visits for managing adverse events as needed. All visits should include safer sex and HIV risk reduction counseling and provision of male condoms to all subjects.

[10] See the CONRAD/World Health Organization *Manual for the Standardization of Colposcopy for the Evaluation of Vaginal Products* at http://www.who.int/reproductivehealth/publications/rtis/RHR_04.2/en/index.html.

In addition to evaluating genital toxicity in women, sponsors should conduct male tolerance studies to identify penile toxicity. Ideally, penile safety data should be obtained before dosing sexually active women in phase 1 trials.

c. Safety in specific populations

In addition to the general safety considerations discussed previously, this section outlines safety perspectives for specific populations, namely pregnant women and adolescents.

**Pregnant women**

To protect the fetus from research-related risks, microbicide trials have historically excluded pregnant women from enrollment and disallowed women who became pregnant to continue to use the investigational drug product. In the real-world setting, however, an approved microbicide may be used by pregnant women despite lack of data in this special population. We recognize that complete lack of safety data in pregnant women at time of NDA submission is not optimal. Ideally, microbicide safety data in pregnant women should be obtained methodically in a prospective controlled trial setting with careful monitoring of subjects. Because of these considerations, the FDA's thinking regarding the evaluation of women who become pregnant while participating in microbicide trials is evolving. In addition, both the woman and the fetus may stand to benefit from a microbicide that could potentially prevent HIV infection.

In some instances, use of an investigational microbicide may be allowed in women who become pregnant while participating in microbicide clinical trials. The decision to allow use of the drug product in women who become pregnant while participating in microbicide clinical trials depends on the safety and PK profile of the drug product in nonclinical studies and early clinical trials. To assess whether pregnant women should continue drug product use, the FDA will consider the following information in the decision-making process:

- Completed reproductive toxicology studies including data from fertility and early embryonic development study, the embryo-fetal development study, and the pre- and postnatal development study.
- Completed genotoxicity studies
- Chronic toxicity studies in two species to support the duration of exposure in human trials
- Data on systemic absorption of the microbicide in nonpregnant female subjects

Additionally, the microbicide trial design should have the following provisions for women who become pregnant:

- Women who become pregnant during the trial should be re-consented. Information about potential risk to the fetus following microbicide exposure should be included in the original informed consent and discussed again with the pregnant subject. Data collected should include but not be limited to timing of pregnancy relative to length of time on the

investigational drug product, duration of fetal drug exposure, and pregnancy outcome. Women who choose to discontinue the investigational drug product but remain in the trial should be followed for pregnancy and fetal outcome data.

- Pregnant women who choose to continue receiving the investigational drug product in the trial should undergo increased safety monitoring including more frequent visits, laboratory testing, and fetal monitoring. In addition, the protocol should include a toxicity monitoring and safety management plan for pregnant women and their fetuses. Protocol safety monitoring should take into account current standards of antepartum care in the trial countries.

- PK data should be collected in a subset of pregnant women who re-consent and who choose to continue the investigational drug product. Assessments should be performed during pregnancy (at least at one time point in each trimester), in the postpartum period, and during lactation to characterize changes in systemic exposure related to any alteration in local absorption.[11] Data should be obtained at time points in each pregnancy trimester, at a minimum. Protocols should also include, when possible, collection of cord blood for the evaluation of systemic exposure to the fetus at the time of delivery.

- The exposed infant should be followed from birth up to 1 year for collection of data during this time frame. Sponsors should obtain FDA concurrence for the type of data to be collected.

- Women who become pregnant during the trial should be followed in a pregnancy exposure registry such as the Microbicide Trials Network Registry MTN-016.

The FDA's decision on a sponsor's proposal to dose pregnant women will be made on a case-by-case basis.

**Adolescents**

In the United States, high-risk heterosexual contact is estimated to account for approximately 90 percent of transmission in adolescent females aged 13 to 19 years (CDC 2010). In certain countries in Sub-Saharan Africa, HIV prevalence is estimated as high as 20 percent among females aged 15 to 24 years (UNAIDS 2011). Local sociocultural norms and biological factors may contribute to the high infection rate in this age group. Younger women with older sexual partners may be less successful in negotiating male condom use. Cervicovaginal differences between adolescence and adulthood, such as the extent of cervical ectopy, may also play a role. In adolescence, a larger zone of ectopy associated with highly vascularized epithelial lining and greater mucosal fragility may increase HIV susceptibility (Moss, Celemetson, et al. 1991).

Conducting clinical trials in adolescents involves important ethical, regulatory, and parental and adolescent consent considerations (Nelson, Lewis, et al. 2010). Generally for drug products

[11] See the draft guidance for industry *Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling*. When final, this guidance will represent the FDA's current thinking on this topic.

approved for adult use, separate clinical studies are needed to establish safety in the pediatric age group, if appropriate.[12] A central consideration in pediatric research is whether the intervention offers the prospect of direct benefit to the enrolled subject. In addition, sponsors should consider the level of risk associated with the intervention (e.g., an intervention that involves greater than minimal risk must offer the prospect of direct benefit to the individual subject and meet certain conditions to involve children as subjects (21 CFR 50.52; see also 21 CFR part 50, subpart D)). Other influential factors include justification of the intervention in the context of disease severity, comparability of the intervention to available alternatives, and past experience for a drug product or the class. Specifically for vaginal microbicides, key considerations in the decision-making process include the serious and life-threatening nature of HIV disease, relatively higher HIV prevalence among adolescents, the likelihood of drug product usage after approval, and the safety profile and efficacy of the drug product.

After approval for adult use, a vaginal microbicide may be used by individuals younger than 18 years, even in the absence of safety data in adolescents. Adolescent safety data should therefore be collected before microbicide approval. Sponsors should consider a two-stage approach whereby initial safety data are collected from older subjects 16 to 18 years of age, followed by recruitment of adolescents younger than 16 years, depending on the clinical needs and pediatric research requirements of the participating trial sites. Sponsors should make every effort to submit safety data from older adolescents with the NDA submission.

Retention in trials and adherence to the drug product are challenges inherent to this age group that should be taken into consideration. Sexual practices vary by region; therefore, sponsors are strongly encouraged to obtain some of their data from adolescents in the United States.

In addition, adolescents are also at risk for pregnancy. Therefore, the considerations discussed in the previous section regarding pregnant women apply to adolescent subjects who become pregnant as well.

d. Other safety considerations

This section focuses on additional safety considerations such as assessing safety following rectal application of semisolid microbicide preparations, and safety in the postmenopausal age group.

**Rectal safety**

Vaginal and rectal compartments differ in several respects including structural anatomy, local epithelial lining, and the population of target immune cells (Poles, Elliott, et al. 2001). As a result, a microbicide shown to be safe and effective for vaginal use should not be assumed to be safe or effective with rectal administration. Use of an unsafe drug product may be deleterious if it increases HIV susceptibility through irritation or breakdown of the more fragile rectal mucosa. After approval for vaginal use, microbicides may be used by women and men off-label rectally with the intention of preventing infection; therefore, rectal safety data for semisolid microbicide

[12] For the purposes of this guidance, reference to pediatric subjects includes only the adolescent age group.

formulations should be available at the time of drug product registration to provide information on any potential significant safety concerns.

Gastrointestinal (GI) toxicity or anorectal toxicity may be caused by the active ingredient, excipient, or physical attributes of the drug product such as osmolarity. Sponsors should conduct rectal safety trials in healthy adult men and women. Subjects with underlying anorectal or GI conditions including evidence of inflammation at screening anoscopy, history of gastrointestinal bleeding, or untreated rectal STIs should be excluded. Trials should initially evaluate single or multiple rectal doses in subjects who are not planning to engage in anal intercourse for the trial duration. Initial trials should include a minimum dosing duration of approximately 7 to 10 days. Rectal application of lubricants and suppositories or rectal douching should not be allowed. Subjects should be monitored for symptoms and signs of anorectal, GI, and systemic adverse events. Safety laboratory testing should include routine safety parameters such as complete blood count, liver, and renal markers. Lower GI endoscopy should be conducted for visual inspection of mucosal toxicity.

Sponsors should consider drug product discontinuation in subjects developing GI or abdominal adverse events, and evaluations exploring potential drug toxicity should be undertaken in consultation with a gastroenterology expert. The protocol should include an adequate safety monitoring plan as well as individual and trial stopping criteria. Nonclinical safety findings and the overall clinical safety profile should be used as guides in making the decision for longer duration safety trials. Plasma drug levels should be determined because systemic exposure with rectal administration may not mimic levels attained with vaginal use.

Randomized, double-blind, and placebo-controlled trials are preferred. Until data supporting placebo effects of hydroxyethyl cellulose (HEC) gel in the rectal compartment are available, safety comparisons with HEC gel should be interpreted with caution. Variations in osmolarity have been shown to affect rectal mucosal integrity (Fuchs, Lee, et al. 2007). Physical attributes such as osmolarity and pH of the placebo gel should match the microbicide gel being evaluated.

**Safety in postmenopausal women**

Microbicide clinical trials typically enroll sexually active adult women up to the age of 40 or 45 years. However, in the United States, the incidence of new HIV infections has risen in women over the age of 50. Postmenopausal women experience thinning of vaginal mucosa and increased expression of cervical CCR5 receptors (Meditz, Moreau, et al. CROI) that may enhance susceptibility to HIV infection. An approved vaginal microbicide likely would be used in women of all ages; therefore, sponsors are strongly encouraged to collect safety data in this population. Safety, tolerability, and PK data can be collected in a separate trial or by allowing limited enrollment of older women, including postmenopausal women, in phase 3 trials or in a separate trial.

## B. Specific Considerations for Efficacy Trials

### *1. Trial Design, Randomization, and Endpoints*

Microbicide efficacy trials should be randomized, double-blinded, and conducted across multiple sites. HIV seroconversion should be the primary endpoint. Demonstrating reduction in HIV seroconversion requires phase 3 trials with large sample sizes. Phase 2 trials, which do not have sufficient power to show differences in seroconversion, can be conducted to obtain safety data before initiation of large phase 3 trials. For logistical reasons, such as maintaining trial sites and maintaining continued enrollment, phase 2 and phase 3 trials can be combined, with a phase 2b lead-in as an initial part of a phase 3 trial. New infections and person-years of exposure obtained in the phase 2 lead-in portion can contribute to the safety and efficacy of the phase 3 portion. Safety and tolerability from the first several hundred women enrolled in the phase 2b lead-in should be evaluated before accrual in the phase 3 portion is initiated. If seroconversion endpoints from the phase 2 lead-in portion are unblinded and evaluated before starting the phase 3 portion, then statistically appropriate methods should be used for combining the results of the phase 2 and phase 3 data. This design offers the advantages of enrolling fewer new subjects than if the phase 2 and phase 3 trials were conducted separately, and of allowing more safety evaluations before expanding the trial enrollment.

### *2. Choice of Comparator*

We recommend a vaginal microbicide placebo as the comparator in efficacy trials when investigational drug products are added to a background of other HIV prevention modalities such as condoms, counseling, and even oral PrEP (as deemed appropriate and acceptable by local jurisdictions; see section III.A.4., Efficacy Considerations). The vehicle (or excipient) component may not serve as an acceptable placebo unless it is known that there are no beneficial or harmful effects resulting from the vehicle. Clinical data support HEC gel as an acceptable placebo because outcomes in the HEC gel arm were shown to be no more than 2.4 percent worse than the *condom-only* arm (or *no-treatment* arm) in HIV prevention trial HPTN 035 (Karim, Richardson, et al. 2011).

Following approval of a vaginal microbicide, an active-controlled noninferiority trial design comparing the candidate microbicide to the approved microbicide could be considered appropriate. A noninferiority design depends on the ability to define the magnitude of the contribution of the new active control such that a reliable noninferiority margin can be calculated.[13]

Designing a trial using oral emtricitabine/tenofovir as a comparator will be challenging. A superiority trial will likely need a large number of subjects to demonstrate a treatment effect in the setting of even moderately good adherence. A noninferiority comparison to oral emtricitabine/tenofovir presents methodological challenges because of uncertainty of the assay sensitivity of oral emtricitabine/tenofovir as an active control. In previous trials of oral

[13] See the draft guidance for industry *Non-Inferiority Clinical Trials*. When final, this guidance will represent the FDA's current thinking on this topic.

emtricitabine/tenofovir the overall preventive treatment effect ranged from 0 to 75 percent depending on subject adherence (Grant, Lama, et al. 2010; Baeten, Donnell, et al. 2012; Thigpen, Kebaabetswe, et al. 2012; Van Damme, Corneli, et al. 2012). Given this historical data, defining a noninferiority margin will be problematic. Sponsors considering an active-controlled noninferiority design should discuss protocol proposals with the FDA well in advance of trial initiation. Use of a future-approved vaginal microbicide as an active control could result in similar methodologic challenges as for oral emtricitabine/tenofovir depending on the effectiveness (and associated confidence intervals) of the approved vaginal microbicide in previously conducted trials.

*3. Enrollment Criteria*

Healthy, non-HIV-infected, sexually active adult women at high risk of acquiring HIV should be enrolled in phase 3 trials. Phase 2 trials also should enroll sexually active subjects. It may be reasonable to enroll moderate- to high-risk subjects in some phase 2 trials to obtain safety data in the target population early in development. In particular, enrolling high-risk subjects is appropriate with the phase 2b lead-in design for reasons discussed previously (see section III.B.1., Trial Design, Randomization, and Endpoints).

Screening evaluation should include medical history, physical examination including pelvic examination, and the following laboratory tests:

- HIV serology
- Serum hematology and chemistry profile
- Urine or serum beta human chorionic gonadotropin
- Testing for STIs, bacterial vaginosis, and vaginal candidiasis
- Papanicolaou smear

At least two negative HIV serology test results are necessary to confirm lack of seroconversion before trial entry. Samples for reverse transcription (or transcriptase) polymerase chain reaction (RT-PCR) testing should be obtained and stored at screening and baseline visits (see section III.C.1., Clinical Virology).

Subjects diagnosed with treatable STIs should receive appropriate treatment and these subjects can be considered for enrollment following resolution of infection. Subjects should not be pregnant and should be willing to prevent pregnancy for the trial duration. Tampon use should not be considered an exclusion criterion.

*4. Trial Procedures*

HIV seroconversion data, as measured by an approved HIV antibody assay, should be obtained through monthly testing. Sponsors should conduct safety evaluations at scheduled intervals as discussed previously. Data pertaining to type and duration of hormonal contraception used should be obtained as part of concomitant medication assessment to allow analysis (subgroup or sensitivity analyses) for any effects of hormonal contraception on microbicide safety or efficacy. Data related to sexual behavior, coital frequency, condom use, microbicide adherence, and

tampon use should be obtained through interviews, subject diary cards, or other methods for obtaining data for self-reported behaviors. Subjects who seroconvert during the course of the trial should be referred for HIV treatment according to the local standard of care.

*5. Trial Duration*

All enrolled subjects should be followed for a minimum period of 12 months and should be followed until the last enrolled subject completes the trial and at least 50 percent of the subjects have received 24 months follow-up. Data reflecting safety over a dosing duration of at least 12 months is important because an approved microbicide may be used indefinitely and new safety concerns from chronic exposure may arise. Longer duration data also captures drug product adherence, which may reduce over time with diminishing effect as observed in some biomedical prevention trials (Karim, Karim, et al. 2010; Grant, Lama, et al. 2010). We do not recommend large trials of short duration because they are not as informative with respect to longer term use.

If interim analyses suggest the targeted number of HIV seroconversions may be reached in advance of the recommended duration of follow-up, sponsors are advised to engage in discussions with the FDA before making decisions about trial termination. Before trial termination, sponsors should provide the FDA with estimates of the exposure including the number of subjects with 12, 18, and 24 months follow-up at the time of intended trial termination. Estimations should account for expected lost-to-follow-up and other anticipated reasons for subject discontinuation.

*6. Statistical Considerations*

a. Endpoint analysis

The primary endpoint should be HIV seroconversion rate per person-year of drug product use. Drug product use should be calculated as the time from provision to the subject of the investigational drug product or placebo until the time when the subject has completed or been discontinued from the trial. Drug product use should not be adjusted for actual use or compliance. Calculations based on person-years of drug product use are preferred to the absolute seroconversion rate because the former accounts for differential dropout rates between arms. In the event of markedly different dropout rates between arms, sensitivity analyses should be provided. Cox proportional hazards regression or Poisson model analysis generally are accepted methods of analysis. Cox proportional hazards regression also can be used with adjustment for protocol-specified baseline covariates. Survival curves and hazard curves should be plotted to ensure absence of convergence or crossover in hazard rates.

b. Strength of evidence

Sponsors should provide evidence from at least two independent clinical trials, each convincing on its own, to support drug product approval.[14] A statistically significant treatment effect

[14] See the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.

compared to control for a superiority trial is a two-sided p-value less than 0.05. Trials with strong internal consistency increase confidence whereas lack of consistency reduces confidence in the result. Conducting two independent trials simultaneously (or nearly so) may be feasible and could avoid potential ethical difficulties if one trial finishes first and shows a statistical significant treatment effect.

Data from a single large phase 3 trial also may be acceptable. Formally, two independent trials each statistically significant at the two-sided 0.05 level provide a strength of evidence equivalent to a single trial statistically significant at the two-sided 0.001 level. However, accepting data from a single large trial is contingent on several variables, including the generalizability of results to a broader population and internal consistency across subgroups and sites within the trial. Sponsors are advised to refer to FDA guidance for details.[15]

Large sample sizes and other challenges with conducting HIV prevention trials may provide an incentive for microbicide sponsors to combine efforts toward collaborative trials. A collaborative trial design evaluating multiple investigational drug products offers the advantage of a single control arm serving as comparator for each drug product. Increasing the control arm size increases the power to show effect for the individual investigational drug product. This design also permits the evaluation of combination products. Safety and efficacy comparisons between microbicides can provide additional useful information.

c. Adherence

Male condoms (or other proven prevention interventions) are expected to reduce HIV transmission; therefore, HIV infection is likely to occur more frequently in subjects not using condoms (or another intervention) irrespective of the trial arm. A larger treatment difference is expected among subjects compliant with the microbicide but not compliant with condoms in case of an efficacious drug product. Secondary analyses in this subgroup, defined based on post-randomization assessments of drug product adherence, may provide supportive evidence of efficacy. A compliance-based secondary analysis demonstrating efficacy would not be considered as a refutation of primary intent-to-treat analysis that failed to demonstrate efficacy.

Self-reports of drug product use alone are not considered to be a reliable measure of adherence. Trials should incorporate objective methods such as plasma or tissue drug levels in the case of systemically absorbed agents or residual drug levels in drug-device combinations to provide estimates of drug product use over time. Data for adherence in the placebo arm, for example by measuring levels of an inert taggant, can allow for sensitivity analyses.

We do not recommend drug product adherence incentives, other than coaching and counseling, because incentives will not be available after the drug product is on the market. A trial using them could exaggerate potential benefit. Incentives that encourage subjects to return for trial visits or maintain contact with site staff are acceptable because these ensure data collection in subjects both on and off their assigned treatments.

[15] Ibid.

d. Interim analysis and data monitoring committee

The plan for interim analyses to assess futility and safety should be finalized before trial initiation, and included in the statistical analysis plan. Based on interim findings, a trial may be terminated early for futility if the conditional power is low. Interim findings such as rate of condom usage or specific local practices affecting HIV transmission rate should guide sample size adjustments in an ongoing trial. Such increases in sample size also should be made in accordance with accepted guidelines for adaptive trial design as documented in the published statistical literature on sample size changes. Safety concerns, including a greater number of HIV seroconversions in the investigational arm, should influence considerations for continuing enrollment or halting the trial. Interim analysis results should be reviewed by an independent data monitoring committee to avoid an effect on trial conduct or recruitment. A detailed charter with the composition of the committee members and the operational details should be provided for FDA review.[16] Sponsors should remain blinded to individual subject and investigator data.

e. Missing data and sensitivity analysis

The sponsor should minimize lost-to-follow-ups and other types of missing data with appropriate planning, including use of incentives that do not interfere with the clinical trial interpretations.

In addition to the analysis mentioned in section III.B.6.a., Endpoint analysis, sponsors should perform sensitivity analysis where all lost-to-follow-ups are imputed by the placebo arm hazard.

*7. Combination Products*

This section discusses combination products, including drug components. Specifically, products including two or more microbicide drug products or microbicide-device products are discussed. Sponsors are encouraged to refer to other FDA guidance for developing combination products.[17]

In general, the following information evaluating the combination microbicide is needed before efficacy studies of a combination product: cell culture combination activity data, nonclinical toxicity for each drug, human safety data from clinical trials for each drug, information supporting selection of proposed doses, and drug-drug interaction data (if applicable). If overlapping toxicity is observed in nonclinical studies, then nonclinical toxicity studies with the combination product may be necessary. Trial designs should include provisions for demonstrating the contribution of each component to the desired effect. Establishing the contribution of each component generally can be accomplished using factorial designs or modified factorial designs. Because the development pathway depends on the specific drugs combined, the approach may vary for different types of combination products. We encourage sponsors to discuss their specific combination product early in the development program.

[16] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*.

[17] See the guidances for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations* and *Codevelopment of Two or More New Investigational Drugs for Use in Combination*.

If one of the components of the combination is marketed as the same vaginal formulation and dose, regulatory requirements may not follow the paradigm outlined above; therefore, sponsors are advised to seek FDA input early in the development process.

Additional considerations for microbicide-device combinations and combinations for multiple indications are discussed below.

a. Vaginal microbicide plus device

Examples of microbicide-device combination include a microbicide combined with a condom, cervical cap, or diaphragm. A microbicide-device combination will be reviewed by both CDER and CDRH; the *primary mode of action* of the combination product will determine which Center has the lead. Both Centers work together through the review process by providing expertise for individual components of the combination. The OCP has a formal product jurisdiction process that can be initiated by submitting a Request for Designation in cases where the lead Center is unclear.[18] In some combinations, the sole function of the device is drug delivery. For this type of product, the primary focus of review will be the active microbicide component.

As previously mentioned in section III.A.1.c., Other nonclinical studies, sponsors should conduct studies evaluating effects of the microbicide on the integrity and function of the device. Stability data for the combination product will be needed if the microbicide formulation used in the microbicide-device combination is different from the stand-alone microbicide. Sponsors should also consider biocompatibility testing on the device with the active drug component.

b. Combination product intended for multiple indications

Developing combination products where each constituent is intended for a different function or indication (e.g., HIV prevention plus contraception) involves complex regulatory considerations. A key consideration for such a multi-indication combination product is whether individual components are investigational or marketed for the respective indication being pursued. If a component is an unmarketed investigational drug, sponsors should consider whether the drug will be approved as an oral formulation or as another vaginally administered formulation for the indication being pursued. We anticipate that a combination product seeking multiple indications will need input from multiple CDER divisions, each providing regulatory expertise for the specific indication.

The development pathway for multi-indication combination products involves unique and complex regulatory challenges. Because regulatory advice depends on combination product characteristics and consultations within CDER, sponsors are encouraged to approach the FDA with questions for their specific combination product and the type of indications they plan to pursue.

[18] See the guidance for industry *How to Write a Request for Designation (RFD).*

*8. Risk-Benefit Considerations*

For the overall risk-benefit assessment, the totality of data should be considered. Benefit in HIV prevention trials should be measured as the percent reduction in HIV transmission during the trial period. Microbicide efficacy trials should be powered to demonstrate at least a 33 percent reduction in HIV seroconversion. Lower rates of reduction in a clinical trial may not translate into a clinically relevant effect because lower rates of adherence or other factors with real-world use may further reduce the actual risk reduction. However, we recognize that lower reductions may have an effect on transmission rates in high HIV prevalence areas. The percent reduction in HIV and the toxicity profile of a microbicide are critical in the decision-making process. Other considerations in deciding risk-benefit include the potential for behavioral disinhibition in the real-world setting, including condom migration (decrease in condom usage secondary to increased microbicide uptake), that can adversely affect transmission rates. Behavioral data, rates of other STIs, and frequency of self-reported condom use collected in trials include the types of data important for evaluation for the final assessment. Resistance development may be an additional concern, particularly for a systemically absorbed antiretroviral drug product.

## C. Other Considerations

*1. Clinical Virology*

Sensitivity and specificity of all assays used to verify HIV status should be validated for a panel of viral isolates representing the most common circulating strains endemic to the trial region. Sponsors should collect and store baseline samples for RT-PCR for all subjects. Testing of stored baseline/screening samples with RT-PCR should be performed to confirm the infection status of subjects who seroconvert during the trial. Verification by RT-PCR is necessary because the antibody assays typically used for baseline analyses (e.g., assay for anti-HIV antibodies) lack the sensitivity of the RT-PCR assay for detecting acute infection. HIV-positive subjects missed by the screening HIV assay should not be considered new seroconversions and should be excluded from the primary analysis.

For a microbicide containing an antiretroviral drug, viral isolates from subjects who seroconvert should undergo genotypic testing. Microbicide failure in these subjects may represent selection and enrichment of resistant HIV-1 variants. This selection could occur during local replication within the vaginal epithelium or during systemic replication, even if there is poor bioavailability. When possible, isolates from a subject's partner also should be genotypically characterized to assess the potential for transmission of resistant virus. If analysis of HIV-1 isolates identifies novel substitutions not previously analyzed during nonclinical resistance studies, the substitutions should be phenotypically characterized.

*2. Additional Clinical Pharmacology*

In vivo drug interaction studies should be considered with the candidate microbicide and commonly used vaginal drug products, including the contraceptive ring (e.g., Nuvaring) and commonly used antimicrobials (e.g., metronidazole vaginal suppository or gel), to ensure local release characteristics and systemic exposure, where applicable, are not adversely affected by co-

administration. The drug interaction data collected should be applicable to the U.S. population and U.S. medical practice. Preferably, all relevant drug interaction studies would be completed before conduct of large phase 2b or phase 3 trials to allow use of these drug products in the trials.

Large efficacy trials should incorporate a PK substudy to allow characterization of local and, if applicable, systemic microbicide exposure in women during actual conditions of use. In addition, PK samples should be obtained from all women at trial visits at which HIV testing is performed and the samples archived for future analysis. Because microbicides can be developed with various coitally dependent and coitally independent dosing schemes, sponsors should discuss the sampling schedule with the FDA. Time of previous doses and the time of the sample collection should be recorded for all PK samples. In the event of seroconversion, all samples for the seropositive subjects should be analyzed and compared to all samples for a matched seronegative cohort. Drug concentration data obtained from a large clinical trial may be useful to evaluate dose, for assessing adherence patterns, and for further analysis in the event of a failed trial.

*3. Chemistry, Manufacturing, and Controls*

Sponsors and applicants should refer to FDA and ICH quality guidances for industry for general chemistry, manufacturing, and controls (CMC) recommendations for drug substance (active pharmaceutical ingredient) and drug product (finished dosage form). Drug product manufacture must be in compliance with current good manufacturing practice requirements (21 CFR parts 210 and 211). CMC considerations specific to vaginal microbicides are discussed below.

Sponsors should conduct formulation studies to evaluate drug product attributes that affect microbicide quality and performance. Attributes that may affect drug product retention and distribution in the vagina or have effects on vaginal epithelium should be evaluated (e.g., drug product solubility at different pH environments, drug product stability, rheological characteristics, adhesion of the vehicle). The ability of the formulation to support the growth of pathogens should be evaluated (e.g., *Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans*, and *Escherichia coli*). Biocompatibility studies should be conducted for vaginal ring microbicides. Attributes that may affect release rate of the active ingredient such as solubility, solid-state form, or particle size of drug substance should be evaluated.

In addition, manufacturing parameters potentially affecting drug product performance should be identified. Drug product formulations that are not inherently antimicrobial should include antimicrobial preservatives to protect them from microbiological growth or from microorganisms that are introduced inadvertently during or subsequent to the manufacturing process (United States Pharmacopoeia General Chapter <51>). Preservative effectiveness studies should be conducted and the drug product formulated with the minimum specified content (or less) of preservative. Sponsors should evaluate the safety, suitability, and performance of the proposed container closure system and delivery system (e.g., vaginal applicator).

Drug product specification should include tests for universal attributes such as identity, strength, and impurities. Depending on the specific dosage form, additional tests should be included in the drug product specification (e.g., viscosity, pH, particle size distribution, homogeneity

assurance, dissolution or melting rate, in vitro release rate for controlled-release drug products, and mechanical integrity test including tensile strength for vaginal rings). Testing for microbial limits also should be part of the drug product specification. If the active ingredient is a polymer, a test should be included for molecular weight distribution (e.g., size-exclusion chromatography). If the drug product contains a preservative, a test for preservative content should be included.

In vitro release testing has been shown effective in assessing the drug product quality and performance over time for certain semisolid dosage forms. However, sponsors should not use in vitro testing as a surrogate for in vivo bioavailability or bioequivalence, unless an in vitro/in vivo correlation can be developed and validated. Further, in vitro release testing generally is not considered an appropriate measure for drawing comparisons between different types of semisolid formulations (e.g., cream versus ointment from the same or different manufacturer) or in comparison of similar formulations across different manufacturers. Sponsors are reminded that the formulation evaluated in phase 3 trials should be identical to the formulation proposed for marketing.

The stability profile for the drug product should be established under long-term and accelerated storage conditions using analytical methods capable of detecting physical changes and chemical degradation. The microbicide should remain stable at a wide range of pH including normal vaginal pH. Data from initial stability studies should be provided to support the dosing duration of the proposed clinical trials. Stability data supporting a proposed expiration date for the commercial drug product are recommended at the time of NDA submission.

*4. Condom/Device Function Studies*

Condom function studies (clinical trials evaluating effects of a microbicide on the failure rate of condoms) may be needed for certain microbicides and microbicide/device combinations. As mentioned previously in section III.A.1.c., Other nonclinical studies, results from nonclinical compatibility tests will guide the need to conduct clinical trials in this area. Sponsors are strongly encouraged to seek input from the FDA regarding the need for condom function studies and the proposed study design. If a clinical trial is needed, sponsors are advised to plan trials based on appropriate methodology (Taylor 2009).

*5. Labeling Considerations*

The label should emphasize that the drug product is intended for vaginal use only, and that efficacy with oral and rectal use are not established. Labeling should include concerning findings in rectal safety trials to convey toxicity issues with potential rectal use. For vaginal ring drug products, a label comprehension study may be needed to ensure instructions for intravaginal ring use are appropriate for the U.S. population. For vaginal gel drug products using an applicator, similar studies evaluating end-user ability to correctly apply the drug product should be conducted before approval. Because a microbicide may not always be effective in preventing HIV acquisition and may not offer any protection against STIs, we anticipate that these drug products will be used with other prevention measures (such as condoms) as part of a comprehensive prevention strategy. The product labeling should adequately convey this

concern. In cases where the results of nonclinical condom compatibility studies, condom function studies, or other device compatibility studies demonstrate that the microbicide or microbicide/device combination has a deleterious effect on condoms or mechanical barrier contraceptives, the labeling should state that the microbicide or microbicide/device combination should not be used with such devices accordingly.

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