CENTER FOR DRUG EVALUATION AND RESEARCH

Guidance for Industry

The FDA published Good Guidance Practices in February 1997. This guidance was developed and issued prior to that date.

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

GUIDANCE FOR DEVELOPMENT OF VAGINAL CONTRACEPTIVE DRUGS

(January 27, 1995)

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This document is an informal communication under 21 CFR 10.90 (b)(9) that represents the best judgement of the Division of Metabolism and Endocrine Drug Products at this time. This document does not necessarily represent the formal position of the Center for Drug Evaluation and Research or the Food and Drug Administration, and it does not bind or otherwise obligate the Center or Agency to the views expressed.

This Guidance is intended to facilitate the development of vaginal contraceptive drug products.

For development of nonoxynol 9 and octoxynol 9 products previously regulated under the Dec. 12, 1980 "establishment of a monograph" please refer specifically to the chemistry requirements (see below) and the Phase II/III section of the Clinical Requirements (Page 5).

CHEMISTRY REQUIREMENTS

Presentation of identity, purity, strength, manufacturing process, and some stability data of the bulk drug and final dosage form is required for an adequate chemistry review, along with meeting Good Manufacturing Procedure (GMP) standards. Much of this information must be submitted with the initial Investigational New Drug (IND) application or cross-referenced to an appropriate Drug Master File. Details demonstrating batch-to-batch consistency of production processes and GMP inspections are usually required later in the process.

PHARMACOLOGY REQUIREMENTS

For nonoxynol 9 and octoxynol 9 products previously regulated under the 1980 "monograph", no pharmacology/toxicology studies are necessary for submission of a New Drug Application (NDA).

The toxicology testing requirements, noted below, pertain to vaginal contraceptives. All recommendations are subject to discussion with the Division of Metabolism and Endocrine Drug Products for modification, if needed. For those products intended for use in STD prevention, additional testing requirements may be requested by the Division of Anti-Infective Drug Products and/or the Division of Anti-Viral Drug Products, and they should be consulted prior to toxicology testing for that indication.

Necessary Prior to Phase I

A vaginal irritation test in rabbits and one to two week toxicology tests in one rodent and one non-rodent species is necessary prior to Phase I. If rabbits are used for short-term testing, no separate irritation study is required. Primates are preferred for long-term toxicology studies.

All toxicology studies should use three dose levels of drug with the high dose showing some toxicity (it is understood that there may be limits to the ability to achieve a toxic dose). The route should be intra-vaginal.

Reproduction Segment I (fertility and reproductive performance) results are necessary prior to Phase I.

PHARMACOLOGY REQUIREMENTS (continued)

Useful prior to Phase I

A Salmonella typhimurium reverse mutation assay (Ames test), an *in vitro* mutation assay (mouse lymphoma test), and an *in vivo* test for cytogenetic damage in mammalian cells (micronucleus test or bone marrow chromosomal aberrations test) would be useful prior to Phase I. A penile irritation (rabbits) study is also recommended.

PHASE II/III

Toxicology tests in a rodent and a non-rodent species, of a duration at least equal to the intended duration of the clinical study (up to six months in rodent and twelve months in non-rodent), are required.

A pharmacokinetics study in animals must be performed to determine systemic absorption. Serum drug levels to determine half-life, C_{max}, AUC, tissue distribution and metabolite profiles should be presented and compared to human data.

Toxicology tests need to include histopathology on all organs (if drug absorbed).

If the drug is absorbed in humans and the vaginal route of delivery in animals cannot achieve much higher drug blood levels than those seen in women, a one- to three-month toxicology study in one species, with the drug given parenterally or orally, may be requested to produce higher drug blood levels in order to identify all potential toxicities of the drug.

Reproduction Segment II (teratology) results are necessary prior to Phase II/III.

Prior to NDA Submission

Carcinogenicity tests in rats and mice should be completed prior to NDA submission. The drug should be given intra-vaginally for two years and the high dose should be the maximum tolerated dose or the maximum feasible dose.

Segment III reproduction studies are required prior to NDA submission. These studies would include perinatal and postnatal studies in rats.

Circumstances which may make some of this testing difficult (such as oral ingestion during vaginal administration due to grooming habits) are recognized and many of the pharmacology/toxicology requirements are open to discussion and appropriate revision.

BIOPHARMACEUTICS REQUIREMENTS

For nonoxynol 9 and octoxynol 9 products previously regulated under the 1980 "monograph", no biopharmaceutic studies are required for submission of an NDA.

The information and data requirements that are outlined in this section may be completed in Phase I, Phase II, or Phase III, depending upon the individual study design.

Data addressing the extent of systemic absorption and exposure to the product's active ingredient(s) as related to the product's recommended dosage level(s), dosage frequency, and the formulation(s) that is to be marketed are required. If the formulation that is tested in the pivotal clinical efficacy and safety studies is different from the to-be-marketed formulation, an assessment of the comparative exposure would be needed.

For a vaginal contraceptive product where the active ingredient(s) is absorbed systemically, the characterization of the routes of elimination and the metabolic profile of the active ingredient(s) would be needed, along with the determination of the elimination half-life. In view of the intended purpose and site of administration of a vaginal contraceptive, for a product where there is systemic exposure to the active ingredient(s) in females, an appropriate assessment of possible systemic exposure of the active ingredient(s) in males would also be required.

Where warranted and appropriate, an *in vitro* release test should be developed for the vaginal contraceptive product.

CLINICAL REQUIREMENTS

Note: Requirements for nonoxynol 9 and octoxynol 9 products previously regulated under the 1980 "monograph" begin on page 5.

PHASE I

Phase I study protocols should be designed to assess safety. Usually, a single dose study to assess toxicity/irritation, in ten to twenty healthy women, is adequate. These subjects should not be at risk for pregnancy.

The Phase I study is often combined with a pharmacokinetics study (analysis of absorption). This initial protocol may also include post-coital testing at mid-cycle, in women not at risk of pregnancy, in order to get preliminary information concerning potential efficacy of the product.

CLINICAL REQUIREMENTS (continued)

PHASE II/III

For a "new" active ingredient product, not previously marketed in the U.S., more than one study (including one comparative study) is expected with at least 200 women (total) who complete twelve months of use. Safety and efficacy information should be presented. Colposcopic assessments, especially in regard to irritation and ulceration, and bacteriologic measures are also expected in ten to fifteen percent of subjects.

NDAs for nonoxynol 9, octoxynol 9, and additional dosage forms of an approved "new" active ingredient, require efficacy information only. No clinical laboratory testing would be expected other than pregnancy testing (i.e., no requirement for pap smears, etc.). Due to variability in vaginal drug delivery, efficacy data for each formulation is expected. For efficacy only, at least 200 women who either become pregnant during the trial or complete six months is required. Six-month lifetable pregnancy rates should be derived. Information on consistent and correct use of the method should also be provided. Vaginal irritation should be assessed by both subject report and physical exam (including colposcopy when indicated).

The patient population to be considered for a clinical efficacy trial should be non-pregnant females, between the ages of 18 and 35, who have a history of normal menstrual cycles and no history of recent abnormal pap smears, regular coitus, and no history of infertility or conditions which lead to infertility. Subjects should have no contraindications to the product or to possible pregnancy.

There are no specific criteria regarding parity issues, previous methods used, coital frequency, and sexual habits (for example to confirm vaginal intercourse), however collection and discussion of such information is expected.

The clinical trial population should be made up of subjects who plan <u>not</u> to use condoms, but it is accepted that rare or occasional use may be unavoidable. Data on use of other methods should be collected, reviewed and presented.

In terms of requirements for a product for which claims are made regarding efficacy in STD prevention, clinical efficacy studies are necessary to confirm effect against any/all pathogens claimed (*in vitro* studies are insufficient). The specific criteria for such studies will be detailed by the Divisions of Anti-Viral Drug Products and Anti-Infective Drug Products.