DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 351

[Docket No. 80N-0280]

Vaginal Contraceptive Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Proposed Rulemaking

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish conditions under which over-the-counter (OTC) vaginal contraceptive drug products are generally recognized as safe and effective and not misbranded. The proposed rule, based on the recommendations of the Advisory Panel on OTC Contraceptives and Other Vaginal Drug Products, is part of the ongoing review of OTC drug products conducted by the Food and Drug Administration (FDA).

DATES: Comments by March 12, 1981, and reply comments by April 13, 1981.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on December 8, 1978, a report of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products. The first portion of the Panel's review, covering OTC vaginal contraceptive drug products, is published below. The portion covering other vaginal drug products will be published in a future issue of the Federal Register. Under § 330.10(a)(6) (21 CFR 330.10(a)(6)), the agency issues (1) a proposed regulation containing the monograph recommended by the Panel, which establishes conditions under which OTC vaginal contraceptive drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditons

under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel, which have been prepared independently of FDA, are issued here as a formal proposal to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. This document represents the best scientific judgment of the Panel members but does not necessarily reflect the agency's position on any particular matter contained in it. FDA is presently evaluating the Panel's recommendations and conclusions and plans to review carefully all comments and reply comments, and other data submitted in response to this proposal. After FDA has completed that review, the Commissioner will issue in the **Federal Register** a tentative final order that will address OTC vaginal contraceptive drug products.

Although FDA has not yet fully evaluated the Panel's report, the agency shares the Panel's concern that "the contraceptive effectiveness of active ingredients cannot be considered separately from the vehicle, the method of delivery, and the actions of other ingredients in the final product." (See part II. paragraph A., below.) The Panel recommended that FDA require in vitro testing to determine the spermicidal activity of each final formulation prior to marketing. FDA agrees that in vitro testing will provide a qualitative measure of a product's potential effectiveness. The results of such an in vitro test will not, however, adequately describe the quantitative effectiveness of the final formulation when it is used in humans.

Because of the considerable consumer interest in knowing whether each vaginal contraceptive product is effective, the agency is considering various approaches to ensure that those data are available. FDA invites comments and other information on how best to achieve this goal. As explained above, the agency believes that in vitro testing alone is an inadequate measure of a product's effectiveness in human use. Accordingly, it appears that clinical trials of each product or final formulation may be the only certain predictor of its effectiveness in humans. Should FDA decide that clinical trials are necessary to prove the effectiveness of each vaginal contraceptive product, the agency will announce that decision, and the procedures for complying with it, in a separate **Federal Register** notice or in the tenative final order for OTC vaginal contraceptives. A decision that

clinical trials are necessary to establish effectiveness may require manufacturers to submit a new drug application (NDA) for approval or to supplement an existing NDA.

FDA is also aware that there is a strong consumer interest in knowing the actual percentage effectiveness of each OTC vaginal contraceptive product and that the Panel also believed that information on the various levels of effectiveness of vaginal contraceptive agents would be most helpful to the consumer. FDA concurs with the Panel that the most valuable labeling is that which expresses effectiveness in terms of the percent of women for whom the product is effective under described conditions of use. Ideally, this kind of labeling would compare the efficacy of the specific vaginal contraceptive drug product to that of other forms of birth control. However, the Panel placed all comparative effectiveness claims in Category II on the basis that there are no valid studies presently available to support such comparative labeling. In view of the difficulties associated with the testing necessary to support such claims, the Panel further recommended that "if, in the future, a manufacturer desires to label a product with such claims, the substantiating data must be submitted to the FDA through the new drug procedures." (See part III. paragraph C.3., below—Category II labeling.) The agency invites com as to whether quantitative claims effectiveness should be required labeling of vaginal contraceptive di products and, if so, what types of studies should be undertaken to substantiate such claims.

FDA recognizes that the Panel classified the ingredient menfegol in Category I as an OTC vaginal contraceptive and that menfegol has been sold abroad for a number of years. The Panel relied on foreign studies and marketing experience to justify its Category I classification; however, the agency believes that there is no basis for general recognition of safety or effectiveness in this country because menfegol is a new molecular entity, never before marketed as a drug in the United States. Data on such ingredients should be submitted to FDA in a new drug application.

Finally, as announced in this preamble, FDA is particularly concerned that the formulation problems attendant to the manufacture of this class of products may necessitate clinical trials to substantiate claims of effectiveness for each vaginal contraceptive product. Accordingly, the agency has concluded that no drug product containing a new

chemical entity may be marketed OTC until FDA has had the opportunity to evaluate data to establish the safety, and effectiveness of the new product.

FDA has determined that menfegol is a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)) and that the ingredient may not be marketed for use as a vaginal contraceptive until FDA has approved an NDA for a specific product. Any clinical studies on menfegol must be conducted in accordance with section 505(i) of the Act (21 U.S.C. 355(i)) and § 312.1 (21 CFR 312.1) of the regulations.

In accordance with § 330.10(a) ((2) (21 CFR 330.10(a)(2)), the Panel and FDA have held as confidential all information concerning OTC vaginal contraceptive drug products submitted for consideration by the Advisory Review Panel. All this information will be put on public display in the Hearing Clerk's Office, Food and Drug Administration, after January 12, 1981, except to the extent that the person submitting it demonstrates that it still falls within the confidentiality provisions of 18 U.S.C. 1905 or § 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD–510) (address given above).

Based upon the conclusions and recommendations of the Panel, FDA proposes the following:

1. That the conditions included in the monograph, under which the drug products would be generally recognized as safe and effective and not misbranded (monograph conditions), be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

2. That the conditions excluded from the monograph, either because they would cause the drug to be not generally recognized as safe and effective or to be misbranded or because the available data are insufficient to support the inclusion of such conditions in the monograph (nonmonograph conditions), be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the **Federal Register,** regardless of whether further testing is undertaken to justify their future use.

FDA published in the **Federal Register** of May 13, 1980 (45 FR 31422) its proposal to revise the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy,* 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) are unlawful to the extent that they authorize the marketing of

Category III drugs after a final monograph. Accordingly, the proposed regulations would delete this provision and provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, would need to be done during the OTC drug rulemaking process, before the establishment of a final monograph (45 FR 31424).

Although it was not required to do so under *Cutler,* FDA also proposed to stop using the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). Any OTC drug product containing a "nonmonograph condition" would be subject to regulatory action after the establishment of a final monograph. This document, however retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC vaginal contraceptives and other vaginal drug products was issued in the **Federal Register** of May 16, 1973 (38 FR 12840).

The Commissioner appointed the following Panel to review the information submitted and to prepare a report under § 330.10(a) (1) and (5) on the safety effectiveness, and labeling of those products:

Elizabeth B. Connell, M.D., Chairman
Evelyn M. Benson, R.Ph.
Cynthia W. Cooke, M.D.
Myron Gordon, M.D.
William A. MacColl, M.D.
William H. Pearlman,, M.D.
Louise B. Tyrer, M.D.

Two nonvoting liaison representatives served on the Panel. Virginia K. Rosenbaum, B.A., served as the consumer liaison. George A. Braun, Ph.D., served as industry liaison, and in his absence Forrest C. Greenslade, Ph.D., served.

The following FDA employees assisted the Panel: James P. Burns, Jr., Ph.D., served as Executive Secretary

until July 1977, followed by A. T. Gregoire, Ph.D. Armond M. Welch, R.Ph., served as Panel Administrator. Lloyd G. Scott, R.Ph., served as Drug Information Analyst until November 1973, followed by Thomas Gingrich, R.Ph., until April 1975, followed by Anne W. Eggers, R.Ph., M.S., until September 1978. Elaine Euchner, R.Ph., also served as Drug Information Analyst from April 1978 until July 1978; and William Best, R.Ph., Served from July 1978 until September 1978. George Kerner, M.S., served as Consumer Safety Officer from February 1975 until July 1977.

The following individuals consulted with the Panel to offer data in their areas of scientific expertise with OTC vaginal contraceptives and other vaginal drug products:

Nancy Chasen
Robert Choate
John C. Culter, M.D.
Paul A. Fehn, Ph.D.
Matthew Freund, M.D.
Leonard J. Goldwater, M.D.
Forrest C. Greenslade, Ph.D.
Stephen G. Hoag, Ph.D.
Roger Homm, B.S.
Marjorie Horning, Ph.D.
Margaret F. Jones, M.S., M.A.
Ruth Kirschstein, M.D.
S. Robert Kohn, Ph.D.
Eric Kunnas
Donald McNellis, Ph.D.
William Masters, M.D.
Nathan Millman, Ph.D.
John Mothersell
Roger Schnaare, Ph.D.
Daniel Siegel, Ph.D.
Charles Westoff, Ph.D.

The Panel was first convened on August 2, 1973, in an organizational meeting. Working meetings were held on September 28 and 29, October 19 and 20, and November 18 and 19, 1973; January 13 and 14, February 8 and 9, March 8 and 9, March 29 and 30, May 9 and 10, June 6 and 7, July 18 and 19, September 20 and 21, November 8 and 9, and December 16 and 17, 1974; January 23 and 24, February 7 and 8, March 14 and 15, April 27 and 28, June 23 and 24, July 24 and 25, September 18 and 19, November 7 and 8, and December 11 and 12, 1975; February 26 and 27, April 22, 23, and 24, July 22 and 23, August 24 and 25, October 8 and 9, November 19 and 20, and December 16 and 17, 1976; January 14 and 15, March 11 and 12, May 20 and 21, June 22 and 23, July 27 and 28, October 1 and 2, November 4 and 5, and December 15 and 16, 1977; February 3 and 4, March 13 and 14, April 28 and 29, May 19 and 20, June 8 and 9, July 10 and 11, July 31 and August 1 and 2, September 28 and 29, and December 7, 8, and 9, 1978.

The minutes of the Panel meetings are on public display in the office of the Hearing Clerk (HFA–305), Food and Drug Administration (address given above).

No person who so requested was denied an opportunity to appear before the Panel.

On January 23 and 24, 1975, the Panel held a symposium concerning scientific aspects of reproduction and fertility control and invited the following participants:

Gerald Bernstein, M.D., Ph.D.
Richard Blandau, M.D., Ph.D.
Forrest C. Greenslade, Ph.D.
Kurt Hirschhorn, M.D.
Sheldon J. Segal, Ph.D.
Thomas Shepard, M.D.
Richard Stambaugh, Ph.D.
Robert Staples, Ph.D.

A symposium on effectiveness of vaginal contraceptives was held on April 28 and 29, 1978, and included the following participants:

William C. Andrews, M.D.
Gary Berger, M.D.
Gerald Bernstein, M.D., Ph.D.
Ron Gray, M.D.
Bernard Greenberg, M.D.
Michelle Harrison, M.D.
Edna Johnson
Philip Kestelman
Jane Menken, Ph.D.
Harold Nash, Ph.D.
Howard Ory, M.D.
Samuel Pasquale, M.D.
Allan Rosenfield, M.D.
Christopher Tietze, M.D.
Ilene Wolcott

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent information submitted through December 8, 1978, in arriving at its conclusion and recommendations.

In this document the Panel presents its review and proposed monograph for OTC vaginal contraceptive drug products. That portion of its review which deals with other vaginal drug products will be presented in a future issue of the **Federal Register**.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC vaginal contraceptive drug products are set out in three categories:

Category I. Conditions under which OTC vaginal contraceptive drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC vaginal contraceptive drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

Table of Contents for the Preamble

I. Submission of Data and Information

A. *Submissions by Firms.*

Firms and Marketed products

Emko Co., St. Louis, Mo 63147
Emko Contraceptive Foam
Emko Pre-fil Contraceptive Foam
Because Birth Control Foam
Holland-Rantos Co., Inc., Piscataway, NJ 08854
Improved Koromex Contraceptive Jelly, Koromex-A Contraceptive Jelly, Koromex Contraceptive Cream, Koromex Contraceptive Jelly
Julius Schmid, Inc., New York, NY 10019
Finesse Contraceptive Creme-Gel Aerosol, Finesse Contraceptive Creme-Gel Measurettes
Immolin Contraceptive Vaginal Crem-Jel
Ramses Contraceptive Vaginal Jelly
Norwich Pharmacal Co., Norwich, NY 13815
Lorophyn Jelly
Lorophyn Contraceptive Suppositories
Nova Corp. of America, Cos Cob, CT 06807
Flavo-Cept Contraceptive Jelly
Ortho Pharmaceutical Corp., Raritan, NJ 08869
Ortho-Cream Contraceptive Cream
Ortho-Gynol Contraceptive Jelly
Preceptin Contraceptive Gel
Vaginal Contraceptive Foaming Tablets

In addition, the following firms, groups, or individuals provided related information:

Beecham Products, Clifton, NJ 07012
Boric acid, lactic acid
Center for Science in the Public Interest, Washington, DC 20036
Talc
Cosmetic, Toiletry and Fragrance Association, Washington, DC 20005

Talc
Ortho Research Foundation, Raritan, NJ 08869
Selected bibilography on vaginal contraception and therapeutics
Proprietary Association, Washington, DC 20006
Indication language
U.S. Borax Research Corp., Anaheim, CA 92801
Boric acid

B. *Labeled Ingredients Contained in Marketed Vaginal Contraceptive Drug Products Submitted to the Panel.*

Acacia
Alcohol
Benzethonium chloride
Boric acid
Butylparaben
De-ionized water
p-Diisobutylphenoxypolyethoxyethanol
Dodecaethylene glycol monolaurate
Glycerin
Hydroxyethylcellulose
Laureth 10S
Menfegol
Methoxypolyoxyethylene glycol 550 laurate
methylbensethonium chloride
Methylparaben
Methyl polysiloxane
Nonoxynol 9
Nonylphenoxypolyethoxyethanol
Octoxynol
Perfume
Phenylmercuric acetate
Polyoxyethylenenonylphenol
Polyethylene glycol 600 monolaurate
Preservatives
Propylparaben
Purified water
Sodium borate
Starch
Stearic acid
Tragacanth

C. *Classification of Ingredients.*

The Panel has adopted and used the following nomenclature for the ingredients reviewed in this document based on the currently accepted terminology stated in the 1978 edition of "USAN and the USP Dictionary of Drug Names." Any ingredients which do not have names established in USAN will be referred to by names recommended by FDA.

1. *Active ingredients.*

Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate)
Laureth 10S
Menfegol (p-menthanylphenyl polyoxyethylene (8.8) ether)
Mthoxypolyoxyethyleneglycol 550 laurate
Nonoxynol 9 (nonyl phenoxy polyoxyethylene ethanol, polyoxyethylenenonylphenol, nonylphenoxypolyethoxyethanol)
Octoxynol 9 (octoxynol, p-Diisobutylphenoxypolyethoxyethanol, polyethylene glycol of mono-iso-octyl phenyl ether)
Phenylmercuric acetate

2. *Inactive or pharmaceutically necessary ingredients.*

Acacia
Alcohol
Benzethonium chloride
Boric acid
But18paraben (butyl paraben)
De-ionized water
Glycerin
Hydroxyethylcellulose (hydroxyethyl cellulose)
Methylbenzethonium chloride
Methylparben (methyl paraben)
Methylpolysiloxane (methyl polysiloxane)
Perfume
Preservatives
Propylparaben (propyl paraben)
Purified water
Sodium borate
Starch
Stearic acid
Tragacanth

Categorization of Active Ingredients

Active ingredients	Category
Dodecaethyleneglycol monolaurate	III(E).[1]
Laureth 10S	III(E).
Menfegol	I.
Methoxypolyoxyethyleneglycol 550 laurate and nonoxynol 9.	III(E).
Nonoxynol 9	I.
Octoxynol 9	I.
Phenylmercuric acetate and Phenylmercuric nitrate.	II(S).[2]

[1] The term "(E)" refers to effectiveness considerations.
[2] The term "(S)" refers to safety considerations.

D. *Referenced OTC Volumes.*

The "OTC Volumes" cited throughout this document include submissions made by interested persons pursuant to the call-for-data notice published in the Federal Register of May 16, 1973 (38 FR 12840). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after January 12, 1981, in the office of the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fisher Lane, Rockville, MD 20857.

II. General Discussion

A. *Introduction*

At the time of its convening, the Panel first considered its specified mandate and general objectives. It recognized that its primary concern must be the evaluation and categorization of the ingredients under its review as defined by the enabling regulation; however, it was also deeply concerned about the health of women and their offspring, the latter both during intrauterine life as well as after birth. The Panel, therefore, concluded that, as a part of its mandate, it would give special attention to the issues involved in labeling and patient instruction, effectiveness rates, delivery systems, vaginal absorption, fetal and infant damage, mutagenicity, and carcinogenicity.

The Panel believed that it was particularly important for OTC vaginal drug product labeling to explain what benefits consumers could expect from the use of such products. For example, the labeling of contraceptive agents should clearly state that the use of such products is intended for the prevention of pregnancy. Conversely, the labeling of vaginal douches should clearly reveal the probable failure of such products when used for the prevention of pregnancy.

Since proper use is important both in relation to safety and effectiveness, the Panel considered it essential that each vaginal product be accompanied by patient instructions written in a manner easily understood by the average consumer. Inasmuch as the required time that must elapse between application and intercourse can vary from product to product depending upon the dosage form (e.g., aerosol, foam, gel, suppository), the specific instructions will be determined from the data derived from the studies performed for each product.

The Panel concluded that information should be given to the consumer regarding the various levels of effectiveness which can be achieved with the use of vaginal contraceptive agents. The Panel, therefore, defined certain terminology which is essential to a discussion of effectiveness. For the purposes of this document, "method-effectiveness" is defined as that level of effectiveness which is attained in a well-controlled clinical trial utilizing highly motivated volunteers who reportedly use the method correctly with every act of sexual intercourse; "use-effectiveness" is defined as that level of effectiveness which is attained when the method is used by large numbers of subjects not all of whom follow the instructions accurately or use the method each time they have sexual relations; "extended use-effectiveness" is defined as that level of effectiveness which is attained when the method is used by large numbers of women, both correctly and incorrectly, over an extended period of time.

The Panel concluded that the term "theoretical-effectiveness" will not be used as it will not be considered synonymous with "method-effectiveness." The term "theoretical-effectiveness" implies a level of effectiveness not possible to achieve outside the laboratory.

The Panel has concluded that the contraceptive effectiveness of active ingredients cannot be considered separately from the vehicle, the method of delivery, and the actions of other ingredients in the final product. Since

any one of these factors may alter the effectiveness of a Category I vaginal contraceptive ingredient, the Panel recommends that any formulation containing a Category I ingredient be subjected, before marketing, to in vitro testing for spermicidal effectiveness. (See part III. paragraph G. below—Testing Guidelines for Contraceptive Effectiveness).

The Panel also has recognized that OTC vaginal contraceptive drug products might be used by the consumer inadvertently during early pregnancy. Moreover, the products might be used during lactation. The Panel has, therefore, included considerations of fetal and infant safety in this document.

The Panel has considered mutagenic and carcinogenic potentials, a relatively new aspect of ingredient and product safety. Several ingredients under review have been subjected to in vitro and/or in vivo (animal) screening for mutagenic-carcinogenic potential.

The Panel is also concerned about the lack of information on the possible absorption of these ingredients from the vagina into the systemic circulation. It has been well established that many ingredients can be absorbed in this manner. Since the technology required to generate information in this area is now becoming available, the Panel recommends that appropriate vaginal absorption studies be conducted on all of these ingredients wherever feasible.

B. *Data Search*

Prior to the formation of the Panel, the FDA Medical Library conducted a literature search covering relevant American publications published between 1950 and 1973. Additionally, interested people and firms submitted data on the ingredients and products which were the charge of this Panel. After a thorough review of these data, the Panel noted that the majority of the references cited were 10 or more years old. Virtually no studies could be found which had been carried out in accordance with today's standards for the evaluation of possible teratogenic, mutagenic, carcinogenic, or toxic effects of the ingredients in these products. Finally, there was very little statistically valid information available on contraceptive method-effectiveness and almost none on use-effectiveness.

Since there was very little information in both the submissions and the FDA literature search, the Panel conducted its own independent review of the pertinent world literature and asked medical and scientific journals to run advertisements requesting additional data. However, only a limited amount of new material was obtained as a result of these efforts.

In addition, a careful review of completed and ongoing surveys of possible adverse effects of OTC vaginal contraceptive products was conducted. This review suggested that no additional relevant data had been or would be uncovered by these efforts.

The Panel requested help from FDA in order to expand the boundaries of the original literature search. A consultant, Margaret F. Jones, M.A., Biology and M.S., Library Sciences, was employed to review all relevant references on mercury in the world literature.

At the Panel's request, the industry liaison submitted in April, 1974, a listing of articles entitled "Selective Bibliography on Vaginal Contraception and Therapeutics" compiled by the Science Information Division of the Ortho Pharmaceutical Corporation. In addition, the Panel listened to testimony from interested parties and a number of invited consultants.

During the course of its deliberations, the Panel organized two symposia. The first one was held in January 1975, and brought together experts from many fields including female anatomy and physiology, genetics, toxicology, and teratology. The aim of this meeting was two-fold: to review all the current pertinent information and to look at data from ongoing research in these areas.

The second symposium was held in April 1978. The goal of this meeting was to explore four areas of concern to the Panel:

1. *Consumer concerns regarding vaginal contraceptives.* This group of presentations dealt with the need for more detailed labeling, both on the box and on the package insert, presented in language easily understood by the average consumer.

2. *Development of clinical protocols.* The problems encountered in the testing of vaginal contraceptives were outlined and recommendations for further evaluations were presented and discussed.

3. *Trends and data collection.* This portion of the program dealt with the current use of vaginal contraceptives and where and how new data on effectiveness might be generated.

4. *Study design and statistical analysis.* The participants in this section discussed the necessary components of future studies which would lead to more accurate use-effectiveness data.

The Panel invited a group of leading consumer advocates, industry representatives, basic researchers, and clinicians to meet with it to discuss these topics. Each invited guest gave a brief presentation in his or her area of expertise. The speakers, the Panel, and

the members of the audience then broke into four workshops on the same four topics. The following day a summary of the deliberations and recommendations of each group was presented. In this way, valuable assistance was given to the Panel in formulating relevant portions of its report and monograph.

In summary, using every means at its disposal, the Panel attempted to gather and review all of the information available on the subjects under consideration before arriving at its conclusions and recommendations. However, the combined efforts described above served to substantiate the original observation that very little work had been done in this field in recent years.

C. Vaginal Anatomy and Physiology

1. *General considerations.* As the Panel began its deliberations, it soon became clear that the information currently available on the anatomy and physiology of the normal vagina was inadequate, particularly in the area of vaginal absorption of drugs. It, therefore, seemed appropriate for the Panel to begin by outlining what is known at the present time in order to be able to identify those areas in which additional research should be performed.

2. *Anatomy*—a. *Gross anatomy.* The adult vagina varies in length from 7 to 10 centimeters (cm); the back wall is approximately 1.5 to 2 cm longer than the front. The front vaginal wall ends at the cervix uteri where it projects into the vagina. This area is called the anterior fornix. A similar but larger space formed in the back is termed the posterior fornix.

The different areas of the vagina have varying configurations. The lower third of the undistended vagina is star-shaped. It is shapted like an "H" in its middle third and crescent shaped at the top.

The front of the vagina lies next to the bladder and the urethra, and the ureters run alongside the walls of the vagina. In the back, the upper three fourths are in close proximity to the rectum. The lower fourth of the vagina lies next to the anal canal. The supports of the vagina are large bands of tissue that radiate from the lateral pelvic walls to the cervix at the junction of the vagina with the uterus (Ref. 1).

b. *Blood supply*—(1) *Aterial blood supply.* The blood supply of the vagina originates with the uterine arteries which give off descending branches called the cervicovaginal arteries. Several smaller branches go to the cervix, the most prominent joining with similar vessels coming from the opposite side to form the coronary artery of the

cervix. The vaginal arteries divide on the lateral aspect of the vagina and send branches to both the anterior and posterior surfaces of that organ. Branches of the internal iliacs, known as arteriovaginalis, may also supply this region. When this occurs, the inferior vesical artery supplies the middle half of the vagina.

The lower half of the vagina is supplied by branches of the middle hemorrhoidal arteries. The various branches of the arteries supplying the right and left sides of the vagina meet in the midline on the anterior as well as the posterior surfaces to form a single median vessel, the azygous artery of the vagina. The dorsal artery of the clitoris originates from the internal pudendal artery and joins with the vaginal blood supply (Ref. 1).

(2) *Venous drainage.* The venous drainage of the vagina consists of a series of plexuses. In the lower portion of the vagina the drainage commences along the urethra and empties into the perineal veins and the dorsal vein of the clitoris, as well as into the middle hemorrhoidal venous plexus. Most of the venous blood then flows in the internal pudendal veins which communicate directly with the hypogastric veins on the same side (Ref. 1).

c. *Lymphatics.* The lymphatics of the vagina consist of three major groups that are closely related to those of the adjoining organs. The superior group of vaginal lymphatics joins those of the cervix, while the middle group courses along the vaginal arteries toward their origin and terminates in the medial chain of the external iliac nodes. This middle group, which drains the greater part of the vagina, terminates in the hypogastric node at the point of origin of the vaginal artery. Part of the third or inferior group of lymphatics courses upward to join with the middle group and terminates in the pelvic nodes. The remaining channels enter the vulva and drain into the inguinal nodes (Ref. 1).

d. *Innervation.* The superior, middle, and inferior hypogastric plexuses make up the nerve supply of the pelvis. There are very few pain receptor nerve endings in the vagina, although receptors related to temperature are present (Ref. 1).

e. *Microscopic anatomy.* The microscopic anatomy of the mucosa of the vagina is unique both in its structure and in its cyclic response to hormonal stimulation. The epithelium is of a thick (0.15 to 0.2 mm) uncornified stratified squamous type, lacking any glands. A submucosal layer is present which is loose in structure. The larger blood vessels and lymphatics course through

this layer, as well as the few nerves that supply the epithelium.

The muscles of the vagina are continuous with the muscles of the uterus. The outer layer of muscle of the vagina is longitudinal. The inner muscle layer of the vagina is less well-developed and runs in a spiral-like course. The outer layer of the vagina is made up of loose connective tissue and contains the blood vessels, nerves, and lymphatics.

3. *Physiology*—a. *Hormonal influences*. In childhood, the vaginal epithelium is not well-developed. However, with the onset of puberty, the vaginal walls begin to assume their adult appearance in response to the sex hormones. Under the influence of estrogen, the vaginal epithelium differentiates into stratified squamous epithelium consisting of the basal, parabasal, intermediate, and superficial layers. The superficial layer is shed and becomes part of the total vaginal secretion. Maturation of the vaginal epithelium does not occur in the absence of estrogen. Under those circumstances only basal and parabasal cells are seen. This pattern is considered to be atrophic and is found before puberty and after the menopause in the absence of continued stimulation by endogenous and/or exogenous estrogen. In sexually mature women, the presence of unopposed estrogen at midcycle may be indicated in the vaginal smear by the number of superficial cells, a high eosinophilic index (Ref. 2), the presence of spinnbarkheit, and a positive fern pattern in the cervical mucus.

Hormonal influences also play a role in the alteration of cervical mucus. The cervical mucus consists of two main components. The first component is a gel-forming "mucin" composed of macromolecules of glycoproteins condensed into micelles, the arrangement of which varies with the endocrine state. Estrogen stimulates the production of large amounts of thin, watery, alkaline, acellular cervical mucus which demonstrates ferning activity, spinnbarkheit, and sperm receptivity. Progesterone is produced during the luteal phase of the menstrual cycle. It inhibits the secretory activity of the cervical epithelium and produces scanty, viscous, cellular mucus with low spinnbarkheit and an absence of ferning. Spermatozoa have difficulty in penetrating this luteal-phase cervical mucus.

The second component, the cervical plasma between the meshes of the gel, is made up primarily of proteins, salts, and water. At midcyle, when unopposed estrogen is present, the plasma between the micelles has a low viscosity. During this time, the parallel arrangement of the micelles permits the sperm to enter the uterus.

b. *Vaginal secretion*. The Panel is using the term "vaginal secretion" to refer to the fluids formed by the uterus and tubes, to which are added desquamated cells from the superficial layers of the vaginal epithelium, blood, microbial flora, debris from bacterial and cellular cytolysis, and fermentation products occurring primarily as a result of the action of microorganisms on the vaginal epithelial cells (Ref. 3). These, together with other components (e.g., seminal fluid, shreds of fiber from tampons, etc.), form the vaginal secretion as herein defined.

c. *Genital microflora*. The indigenous flora of the vagina produce a constantly changing ecological system. The composition of this ecosystem is affected by many factors, the most important being the sex hormones as evidenced by the sparse microflora found in the atrophic state.

The following groups of organisms have been identified as the major components of the indigenous microflora of the female genital tract (Ref. 4):

Cocci
Coliform
Diphtheroids
Facultative anaerobes
Fungi (including *Candida albicans*)
Lactobacilli (e.g., Doederlein's bacillus)
Micrococcaceae
Trichomonas

It has long been considered that the several strains of lactobacilli are the organisms which produce the normal vaginal environment by maintaining the acid pH of the vagina. In certain pathological states of the vagina, some of the microorganisms overgrow and produce symptoms of discharge, vaginal and perineal irritation, and odor. Other organisms (e.g., *Hemophilus*) which are always considered as pathogens may produce the same symptoms. Because of the wide variety of microorganisms that normally inhabit the vagina, it is difficult to determine which of the microorganisms present may be responsible for pathological conditions. It is also important to know in what relative numbers they need to be present and their relationship to other microorganisms before it can be said that a woman has vaginitis caused by a particular microorganism. This complexity causes problems in medical diagnosis and compounds the difficulty of determining whether a particular therapy is effective in treating vaginitis.

d. *pH of vaginal secretions*. The normal range of vaginal pH is 3.0 to 5.5. There are minor variations in pH of vaginal secretions during the various phases of the menstrual cycle, the secretions becoming less acidic around the time of ovulation and during menstruation. The acidity of the vagina is maintained by the action of lactic acid-producing Doederlein's bacillus on desquamated vaginal epithelial cells which contain glycogen. The glycogen content and the sloughing and renewal of vaginal cells are regulated by ovarian hormones.

The moist acidic milieu of the vagina is essential for the growth of the normal vaginal flora including the Doederlein's bacilli. At the same time the acidic environment provides some measure of protection against overgrowth and invasion by pathogenic microorganisms and against their progression upward through the genital tract. The physiologic protective mechanisms, resulting from hormonal stimulation and the action of Doederlein's bacilli to maintain an acid pH, are optimal during the reproductive era (Ref. 5).

e. *Vaginal odors*. Vaginal secretions have a characteristic odor which varies during the menstrual cycle for any individual woman. In a healthy state the vaginal odor in the nonmenstruating female is slightly acidic. The individual characteristic vaginal odor is frequently changed by alterations of the normal vaginal flora, or by invasion of the vagina by pathogens (e.g., *Hemophilus*). The are no criteria as to what number or type of microorganisms will result in the production of an "unpleasant" vaginal odor, but infection with certain microorganisms produces characteristic odors.

With gas chromatography it is now possible to separate and identify certain components of vaginal contents on the basis of vapor pressures and solubilities (Ref. 6). More than 30 fractions have been obtained from human vaginal secretions on liquid gas chromatography; some of these fractions are odoriferous. Certain short-chain aliphatic acids known as pheromones are found in vaginal secretions. These are produced at the time of ovulation in primates and thus play an important role in determining sexual behavior. It has been postulated that pheromones may play a similar role in humans.

4. *Vaginal absorption of drugs*. In 1918, Macht summarized the human and animal data on the vaginal absorption of drugs (Ref. 7). Since drug assay methods at that time were still quite crude, evidence of vaginal absorption was determined mainly by the production of pharmacological and/or toxicological effects of drugs administered intravaginally. Thus, vomiting was induced with morphine; salivation, with pilocarpine; certain characteristic

cardiovascular effects, with atropine; and violent diarrhea and death, with mercuric chloride.

A number of studies evaluated the amount of systemic absorption of antibacterial agents after their intravaginal administration to human subjects. Rock (Ref. 8) reported the appearance of therapeutic blood levels of penicillin within 1 hour after 100,000 units of penicillin calcium in cocoa butter suppositories were placed in the vagina; these levels were maintained for from 4 to 6 hours. Absorption proceeded more slowly around the middle of the menstrual cycle and was even slower in pregnant females.

The feasibility of administering steroids for contraceptive purposes by absorption from the vagina was first studied by Mishell et al. This group reported that chlormadinone acetate (CMA) was absorbed from silastic vaginal rings (Ref. 9).

Radioactive tracer techniques have significantly improved the precision and accuracy of the evaluation of the vaginal absorption of drugs in both humans and animals. For example, the use of radioactive mercury greatly facilitated the studies on the degree of vaginal absorption of phenylmercuric acetate (PMA) in animals. (See part III. paragraph C.2.a. below—Phenylmercuric acetate.)

In summary, it appears that: (a) Certain drugs undergo systemic absorption when administered intravaginally; (b) the amount of absorption varies with the type of vehicle used for administration; (c) a compound can be absorbed in amounts which produce pharmacological effects, including effects on the fetus (Ref. 10); (d) drugs enter the systemic circulation from the vagina and exert their effects based upon the blood level attained (Ref. 11); (e) the metabolism and distribution of drugs absorbed from the vagina may differ substantially from that resulting from their oral administration; (f) there may be considerable variation in the degree of absorption of a given dose of a drug depending on the characteristics of the individual woman being treated (e.g., age, hormonal balance, the stage of menstrual cycle, the presence or absence of pregnancy, and multiple other factors); and (g) many of the fundamental principles concerning the kinetics of absorption from the vagina and the various factors involved are not known and should be subjects for future investigation.

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D. Drug Evaluation for Safety

The Panel reviewed both OTC vaginal contraceptives and other vaginal drug products. Although that portion of its review which deals with other vaginal drug products will be published in a future issue of the **Federal Register,** this section on safety testing is the same for both classes of drug products. The Panel believes that since all of the ingredients under its review are applied to the vagina, the guidelines for safety testing are identical no matter what the ingredient or vehicle or the drug's intended pharmacological purpose.

1. *General discussion.* A number of studies have shown that the vagina has the ability to absorb or transport certain materials placed within it. Rock, Barker, and Bacon (Ref. 1) have found that penicillin, formulated in cocoa butter suppositories, is easily absorbed from the vagina, ordinarily providing

therapeutic blood levels for 4 to 6 hours. More recent studies have further demonstrated the absorption of compounds from the vagina. Beck, Boots, and Stevens (Ref. 2) have found that bovine milk immunoglobulin is absorbed from the vagina of the baboon, thus indicating that macromolecular weight proteins are capable of passing from the vagina to the blood stream. Rigg et al. (Ref. 3) have discovered that the intravaginal administration of micronized 17-beta-estradiol results in rapid and sustained absorption of the hormone in humans. In the light of these and other studies, the Panel concludes that it is important to study vaginal absorption when evaluating the safety of any vaginal preparation. (See part II. paragraph C.4. above—Vaginal absorption of drugs.) The investigator must be concerned with the safety of the nonpregnant or pregnant user, the conceptus through the embryonic stage, the fetus up to the moment of birth, and the neonate if any ingredient is found to be transmitted through breast milk.

When the Panel attempted to evaluate the safety of ingredients found in OTC vaginal drug products used during the period from fertilization through organogenesis (10 weeks after conception), it found that the available pertinent literature on most of the ingredients under review was extremely scanty. The literature on teratology is replete with reports on studies dealing with the damaging effects of abnormal diets, trypan blue, antimetabolites, hormones, radiation, thalidomide, antibiotics, mercury, and other substances. The list of known teratogens is long, indeed, but the Panel found little information regarding the majority of the ingredients under its review. Additionally, the Panel found that few studies have been concerned with whether or not those ingredients cause other adverse reproductive effects such as infertility and spontaneous abortion.

There is evidence to suggest that the period of greatest susceptibility to teratogens may start as early as the 11th or 12th day after fertilization in the human (Ref. 1). Inasmuch as this is a period during which pregnancy may not be suspected, the Panel recognizes that substances potentially toxic to the conceptus may be inadvertently used during this time. It has been shown that the fetal kidney does not begin to function until about the 14th week after conception and then only imperfectly. Therefore, the question arises of how the fetus handles those chemicals ordinarily excreted through the urine. It is also known that the fetal kidney does not clear drugs as rapidly as the mature

organ (Ref. 2). In addition, the incomplete development of enzyme systems important in the detoxification of drugs further contributes to the inability of the fetus to metabolize or eliminate drugs through the ordinary processes (Ref. 3). It is only shortly before birth that enyzme activity develops to a significant level; even during the first month of life, enzymes are relatively ineffectual as detoxicants. Although there is a considerable clearance of chemicals by the placenta and maternal circulation, the potential still exists for accumulation of toxic substances in the fetal compartment.

Aside from these physiological considerations, the safe use of a drug is affected by the size of the dose, maternal concentrations and clearances, the integrity of the placental-fetal-amnion circulation exchange, the stage of development of the conceptus and the possible interaction with other substances. Some substances have received intensive study, e.g., mercury, thalidomide, hexachlorophene, camphor, antimetabolites, and certain antibiotics and chemotherapeutic agents. However, the etiology of the substantial number of spontaneously aborted or blighted ova observed in early pregnancy remains to be identified. The Panel is concerned that certain of these events may be the result of exposure to supposedly benign substances such as OTC drug products. It, therefore, recommends that any ingredients assigned to Category III for the above reasons be studied in appropriate animal models to determine whether or not they produce adverse effects on the conceptus at any of the three stages of development, and that quantitative assays be carried out on breast milk where indicated.

Many of the ingredients under review have been widely used for a number of years with few reported adverse effects upon women. The Panel is aware of the difficulties that would be involved in obtaining data on the possible rare or hitherto unrecognized side effects of these ingredients (e.g., carcinogenicity) Moreover, most studies on the use of these ingredients have not utilized patient samples of sufficient size, nor have they been of sufficient duration to allow statistically valid determination of these risks.

The Panel's primary concern regarding safety is related to the use of these ingredients during embryogenesis, pregnancy, and lactation and to their possible potential for fetal and neonatal damage. It is important to note that with the exception of mercury compounds, there is no evidence to date which would suggest that these ingredients

under consideration have produced any such damage in the past. However, there are virtually no data on the possible adverse effects upon a fetus at all stages of development. The Panel, therefore, urges that retrospective studies be carried out (under the aegis of either public or private agencies) in order to determine whether or not these ingredients may play a role in producing fetal anomalies.

Certain of the additional studies which the Panel recommends must be conducted first in animals and then in humans. Obviously, testing for acute or subacute (chronic) toxicity can be permitted on animals only. However, local toxic effects (e.g., vaginal irritation) should be ascertained initially on animals and subsequently on humans if negative results are obtained in the animal tests.

The Panel has established guidelines for those tests which it believes to be absolutely necessary for ingredients which have been placed in Category III. It is not the intent of the Panel to require that every Category III ingredient undergo all of the tests outlined below. Rather, the scope of the investigation of the test ingredient would be commensurate with its potential biological hazards as determined by preliminary studies on acute and chronic toxicity. Thus, the investigator is allowed a certain flexibility in planning the protocols with the proviso that the outlined objectives be fulfilled in each instance. The investigator should consult with FDA in outlining these protocols. The Panel recommends that when new information in the future suggests that any ingredient currently in use may produce previously unsuspected maternal or fetal damage, the relevant tests as described below should be required. Finally, all testing procedures must be carried out at a high scientific level which reflects the current state of the art.

2. *Toxicity studies*—a. *Acute*—(1) *Rationale.* A thorough investigation of the acute toxicity of the test ingredient is essential so that potential hazards may be assessed in order to determine the extent of subsequent investigations.

(2) *Animal species.* The tests should be conducted in the rat or mouse.

(3) *Data sought.* The tests should determine the lethal dose for 50 percent of the subjects (LD_{50}). The intravenous route of administration is appropriate for water-soluble ingredients. The intraperitoneal or other parenteral routes are appropriate for water-insoluble or particulate ingredients. The oral route is not recommended because of the highly variable degree of absorption.

b. *Subacute and/or chronic*—(1) *Rationale.* Since virtually all of the ingredients under review are found in products frequently used over an extended period of time, it is essential to look for chronic toxicity.

(2) *Animal species.* The tests should be conducted in one nonrodent species with 12 months of exposure and one rodent species with 24 months of exposure.

(3) *Data sought.* The following should be observed and recorded: Body weight, food consumption, and behavior. Laboratory evaluation should include hemogram, blood coagulation, liver and kidney function tests, and metabolic tests. Gross and microscopic examination of tissues (including liver, kidney, brain, and reproductive organs) should be conducted along with any other appropriate tests.

c. *Local toxicity studies.* Local toxic effects should be ascertained initially on animals and subsequently on humans if negative results are obtained in the animal tests.

(1) *Rationale.* Inasmuch as these products may be used frequently and over an extended period of time, their potential for local irritation and sensitization must be determined.

(2) *Animal species.* The rabbit provides an excellent, albeit highly sensitive, animal model for testing agents for potential vaginal irritation. Up to the present time no reliable animal tests have been developed with screen for vaginal sensitization. An intradermal test on the guinea pig or a cutaneous test (modified Landsteiner) would be appropriate for the preliminary screening and identification of potentially strong sensitizing ingredients.

(3) *Human testing.* The final and only totally valid tests for irritation and sensitization would be those carried out in human subjects.

(4) *Data sought.* Certain classes of vaginal ingredients because of their known pharmacologic actions are particularly suspect in this regard. Routine clinical testing of agents containing detergents or surfactants must be carried out in women under conditions of normal use in order to determine the potential for vaginal and skin irritation. Contract dermatitis, which has been shown to result on occasion from the use of soaps of synthetic surfactants, is an irritation which ranges in severity from mild skin roughening and scaling to actual ulceration.

3. *Metabolic studies*—a. *In vivo*—(1) *Rationale.* Any ingredient which exhibits toxicity during preliminary testing must be further evaluated

because of the possibility of vaginal absorption in significant amounts when the ingredient is used over a prolonged period of time. Accurate assessment of the cumulative potential of the ingredient may be obtained by the systemic administration of the ingredient by the intravenous or other appropriate parenteral route, including the vaginal route. This is to be followed by the determination of the urinary excretion rate and the clearance rate of the ingredient and its major metabolites from various tissues (e.g., blood, liver, kidney, brain, and reproductive organs). The turnover rate and half-life of the test ingredient may then be calculated for the entire body and for various compartments (organs or tissues). Such data would allow prediction of the rate of accumulation of the toxic ingredient on repeated or continuous exposure at various dose levels. The results from the animal studies might then be cautiously extrapolated to chronic human usauge.

(2) *Animal species.* The tests should be conducted in one rodent and one nonrodent species.

(3) *Data sought.* The ingredient and its major metabolites in the various tissues should be chemically analyzed at appropriate time intervals following the systemic administration; clearance rate, turnover-time, and half-life of the test ingredient should be calculated.

B *In vitro.* The proven potential for the toxicity of a given ingredient will make it necessary to investigate the biochemical mechanisms underlying its mode of action. Such data may be obtained form in vitro studies, e.g., determination of the effect of the test ingredient on critical enzyme systems in surviving tissue slices, examination of cellular membrane structure and cell division, etc. Results from these tests would allow further assessment of the potential hazards of the test ingredient.

4. *Vaginal absorption studies—a. Rationale.* Although an ingredient used in a vaginal preparation may prove to be toxic when administered systemically, it may present no hazard if it is not absorbed when applied intravaginally.

b. *Animal species.* At least two species of animals that are not closely related phylogenetically should be tested. Pregnant animals as well as nonpregnant animals at different stages of the estrous cycle should be studied following single and repeated applications of the ingredient. Rats and sheep are excellent animal models for the study of vaginal absorption. Care must be taken in the selection of animal species to be sure that the dosage form of the test preparation is appropriately retained within the vagina. Sheep are particularly useful in such studies

because the gross anatomy of the vagina and the body weight of sheep are similar to those of the human. Rats and rabbits can also be used.

However, certain solid dosage forms are frequently expelled by reflex from the vagina of the rabbit and other species. For instance, dogs expel by reflex a variety of dosage forms, e.g., gels and creams, from the vagina. Liquid formulations may be vaginally applied in most of the above species provided that retention of the formulation for long periods of time is not critical to the experimental design. With these considerations in mind, studies entailing single vaginal applications would be appropriate, e.g., in the rabbit and dog. Nonhuman primates (e.g., rhesus monkey and baboon) would be eminently suitable, but they would need to be restrained so that they could not remove the inserted materials.

c. *Human testing.* Finally, determinations must also be made of the concentration of the test ingredient and its major metabolites in the blood and urine of treated women.

d. *Data sought.* The degree and rate of vaginal absorption of the test ingredient in an appropriate vehicle can be determined by measuring the levels of the ingredient and its major metabolites in blood, urine, and certain body tissues (e.g., liver, kidney, brain, and reproductive organs). The levels thus attained can then be compared with those observed when the ingredient is administered systemically to animals at dose levels which have previously been found to induce toxic or embryotoxic effects. The potential hazards of the vaginal application of the test ingredient and the margin of safety may then be evaluated with respect to the human fetus and the pregnant and nonpregnant woman. Such tests are particularly important since the fetus and the neonate are highly susceptible to the toxic action of chemical pollutants and drugs.

Other components of the vaginal preparation, such as the vehicle, may appreciably affect the rate of vaginal absorption of both the test ingredient itself and of the test ingredient in the final product formulation. Such factors need to be taken into account when studying vaginal absorption rates.

5. *Mutagenicity and carcinogenicity studies.* Tests for mutagenicity and carcinogenicity will be required for certain ingredients about which the Panel has expressed particular concern, even though these ingredients have been in use for a long time without apparent adverse effects.

a. *Background.* Fetal damage may occur if vaginal preparations having

carcinogenic potential are used during early pregnancy. Carcinogenic effects may occur in perinatal or adult life. That transplacental carcinogenesis can occur has been amply demonstrated in animal studies with various classes of carcinogenic agents (Ref. 4); similarly, it has also been demonstrated in the human with the synthetic estrogen, diethylstilbestrol (Ref. 5). However, the carcinogenic agents were not administered by the vaginal route in these studies. Nevertheless, it has been established (See part II paragraph C.4. above—Vaginal absorption of drugs) that in many instances chemicals absorbed from the vagina enter the maternal circulation and are transported across the placenta into the fetal compartment. The fetus (and the newborn) are especially susceptible to the action of chemical pollutants, particularly to carcinogenic compounds. And there seems to be little doubt that during fetal development and early infancy some tissues are more susceptible to certain carcinogens than they are later on in life (Ref. 6). For example, tumors occur in the offspring following treatment of pregnant rats with certain nitrosamides at a dose level that does not produce tumors in the mother.

Safety evaluation of vaginal preparations should take into consideration the earliest stages of pregnancy, e.g., the effects of drugs on the blastocyst (Ref. 7) and the passage of drugs and other chemicals into the uterine fluids and preimplantation blastocyst (Ref. 8). There is little known at present on the effect of carcinogens on the blastocyst.

The Panel is also concerned about the infant who is breast fed by a mother who uses vaginal preparations because an unsuspected carcinogenic agent may be absorbed from the vagina, enter the systemic circulation, and be excreted in the milk. Drugs administered to mothers often appear in the milk (Ref. 9). Indeed, certain drugs (e.g., alcohol, barbiturates, thiouracil, iodine, nicotine from smoke, etc.) pass readily into the milk and, when taken in excessive amounts by the mother, can adversely affect the infant (Ref. 9). Moreover, carcinogenesis via mother's milk has been demonstrated in animal experiments. Pulmonary tumors were induced in mice that were suckled by mothers who received urethan during lactation (Ref. 10). Tumor induction was also achieved with aliphatic nitrosamines in similar studies with the Syrian golden hamster (Ref. 11).

The woman herself must be evaluated, although she may be less susceptible to the action of carcinogenic

agents than is the fetus or infant. On the other hand, she runs the risk of prolonged exposure from the continued use of the deleterious vaginal preparation.

b. *Tests for mutagenicity/ carcinogenicity.* The ultimate and most reliable test of carcinogenicity requires exposure of the test animal to the suspected carcinogen under conditions simulating human exposure (Ref. 12 and 13). The vaginal route of administration would be most appropriate in the opinion of the Panel. Exposure of the test animal, e.g., the rat, should be made during nonpregnancy, early pregnancy, and lactation. The adult, the fetus, and the offspring should be examined for tumor formation. Lifespan studies would be required, or 2-year studies if rats were used.

Alternatives to the lengthy and costly assays for carcinogenic activity outlined above may be sought in short-term predictive tests. The host-mediated in vivo and in vitro combination assay developed by DiPaolo et al. (Ref. 14) at the National Cancer Institute seems particularly relevant to the conditions of human exposure. In this assay the chemical to be tested is injected intraperitoneally into a pregnant animal such as the hamster. Embryo cells from the pregnant hamster are cultured; the primary and secondary cultures are composed predominantly of diploid fibroblasts. The appearance of morphological transformations in these cells is considered to be predictive of the chemical's carcinogenic activity. An in vitro assay procedure similar in principle has been developed by other investigators (Refs. 15, 16, and 17). Cultured embryo cells from untreated pregnant hamsters are exposed directly to the chemical to be tested observed for morphological transformation. DiPaolo et al. (Ref. 18) have shown that the inoculation of hamsters with cells of the transformed colonies results in tumors.

Pienta et al. (Ref. 19) have identified factors which affect the reproducibility of the hamster embryo system. They noted that certain carcinogens need to be metabolized to an active form; therefore, an activation system must be added to the embryo cells in order for the assay to be valid. These and other mammalian cell transformation systems for the identification of potential carcinogens have been reviewed by Krahn (Ref. 20) who concluded that a positive response in the systems currently available indicates that the chemical is potentially hazardous and that testing in more sophisticated bioassays is necessary. The cell transformation systems, on further

development and refinement, may be especially accurate predictors of the carcinogenic potential of chemicals.

Certain other test procedures are used to identify potential mutagens. It should be noted that not all mutagens have been demonstrated to be carcinogens, although most carcinogens are mutagens.

These prescreening tests are attractive because they are rapid, relatively inexpensive, and reasonably easy to perform. The majority of the tests use as end points some form of genetic damage (Ref. 21). The end points include, first, measurement of mutations at individual loci as in the bacterial mutagenic assays, e.g., the Ames test (Ref. 22), and in certain mammalian cell culture systems, e.g., Chinese hamster ovary (CHO) cells (Ref. 23); second, measurement of DNA damage and repair; and third, measurement of clastogenic events including deletions, breakage, and repair of chromosomal material.

The results obtained in the bacterial mutagenesis assays must be interpreted with caution since there are many areas of potential variability in conducting these assays (Ref. 24). Several carcinogens (e.g., diethylstilbestrol and saccharin) found to be negative in the Ames test were detected in the mouse lymphoma mutagenicity assay (Ref. 25).

There are several quantitiative assays for gene locus mutation which use mammalian cell culture systems (Ref. 26). These systems include CHO cells, hamster lung V-79 cells, mouse lymphoma cells, and human fibroblasts and lymphoblasts. The principal steps in the assay procedure are, first, exposure of the cells to a known concentration of the test compound for a fixed period of time; second, incubation to allow fixation of the mutagenic lesion and expression of mutant phenotype; and third, counting the mutant colonies after they grow to macroscopic size.

In vivo tests of mutagenicity in the mouse (Ref. 21) include procedures which measure somatic damage and germ cell damage. Somatic damage is sought in the micronucleus test, in studies of somatic cell cytogenetics and sister chromatid exchange, and in the recessive coat color spot test. Germ cell damage is sought in the dominant-lethal test, heritable translocation assay, studies of sperm morphology, and the germ cell specific locus test. The dominant lethal test might be considered to be irrelevant since by definition dominant lethals pose no general hazard to future generations. However, fetal death or loss by miscarriage, as determined in this test, is not irrelevant

to humans and must be considered in evaluating risk to humans.

The Panel has perused the detailed reports of the proceedings of national conferences (Refs. 12 and 13) on mutagenesis and carcinogenesis testing of chemicals, and has consulted with experts in this area, particularly with reference to vaginal preparations. The Panel shares in the consensus, expressed at the most recent conference on strategies for short-term testing for mutagenesis/carcinogenesis, that a battery approach to testing should be followed (Ref. 13). In this approach, the compound is subjected to several tests. The Panel recommends that at least three of the following types of tests be used in evaluating a vaginal preparation: Bacterial mutagenesis, cultured mammalian cell mutagenesis, cell transformation, DNA damage and repair, and whole animal mutagenesis or chromosomal damage. At least two mammalian cell culture systems that have proved to be useful are described in the review (Ref. 26) briefly discussed above. No single test can be considered in making a reliable final assessment of potential carcinogenicity since all tests may be expected to yield a fraction of false-positive and false-negative results. The Panel recognizes that these test systems are not totally predictive at the present.

6. *Maternal-fetal transfer studies—a. Rationale.* Should an ingredient produce either embryotoxic effects or chronic toxic effects in the pregnant animal, it would be important to determine the rate and magnitude of the transfer of the ingredient and its major metabolites from the maternal to the fetal compartment. These data plus those on vaginal absorption would allow further assessment of the degree of potential hazard to the fetus under experimental conditions simulating normal human usage.

b. *Animal species.* One or more animal species in which chronic systemic toxicity or embryotoxicity has been demonstrated should be studied.

c. *Human testing.* Human "discard" tissues of the products of conception (i.e., placenta, cord blood, amniotic fluid) may be analyzed for the test ingredient and its major metabolites when there is a high degree of suspicion regarding its potentially toxic nature.

d. *Data sought.* Chemical analysis for the ingredient and its major metabolites should be carried out in the conceptus (e.g., fetus, placenta, amniotic fluid) and certain maternal tissues (e.g., blood, liver, kidney, brain, and reproductive organs) following the systemic administration of the ingredient to the pregnant animal. Histochemical studies

may be required to establish the site of localization of the test ingredient in these various tissues.

7. *Teratogenicity studies—a. Rationale.* The test ingredient should be administered systematically (e.g., intravenously or by another appropriate parenteral route) into the maternal compartment during early pregnancy, through the period of organogenesis. It should be given in varying doses so that a threshold dose of embryotoxicity and/ or teratogenicity may be established. This is the logical starting point from which to extrapolate downward in setting a safe tolerance level for drugs that may be used by pregnant women.

If the test ingredient appears to be embryotoxic, maternal and fetal levels of the ingredient and its major metabolites in blood and other tissues should be determined so that correlation of such levels with teratogenicity may be made.

b. *Animal species.* At least two species of animals that are not phylogenetically closely related should be studied, thereby increasing the chance that one species will metabolize the test compound more like the human, thus reducing the uncertainties that stem from the differences in placentation in various species.

c. *Data sought—*(1) *Conceptus.* The calculation of the number and weight of fetuses at different stages of gestation, notation of anatomical malformations, gross and microscopic examination of all tissues (fetus and placenta), and other appropriate tests should be performed.

(2) *Offspring.* The stillborn offspring should be counted and autopsied; morphological and chemical data should be ascertained. Litter size should be noted; and appropriate examinations, which include observations of neurological and behavioral aberrations (e.g., in locomotion and other coordinated motor activities), should be conducted on the living offspring.

(3) *Lactation.* The growth curve of the pups during the suckling period should be charted. Growth retardation would suggest a deleterious effect of the drug on the amount and/or nutritional quality of the milk. Chemical analysis for the test ingredient and its major metabolites in the milk will be required if there are adverse effects on the suckling pups. Surrogate pups from a dam not exposed to the test ingredient should also be used.

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E. Drug Evaluation for Effectiveness

Certain ingredients which the Panel considers to be safe may require studies

demonstrating effectiveness. The ingredients in the products reviewed are all applied to the vagina; for this reason the Panel believes that the guidelines for safety testing can be identical no matter what the dosage form. However, the dosage form would influence the effectiveness of the ingredients significantly. The Panel has established effectiveness testing guidelines for vaginal contraceptive drug products. (See part III. paragraph G. below— Testing Guidelines for Contraceptive Effectiveness.) That portion of its review which deals with the effectiveness testing of other vaginal drug products will be published in a future issue of the Federal Register.

F. Advertising

The Panel is aware that FDA has jurisdiction over the labeling but not over the advertising of OTC drugs. Having completed its review of labeling provided in the submitted data and information, the Panel is concerned that control of labeling alone may be insufficient to assure the safe and effective use of vaginal contraceptives. The Panel, therefore, concludes that the advertising of these products must be carefully monitored by those having the appropriate jurisdiction, and that such advertising should carry over, reflect, or incorporate the approved terms and statements found in product labeling identified in the monograph which specify the indications for use, contraindications, and appropriate warnings to the consumer.

G. Labeling

The Panel has reviewed the general and specific labeling requirements previously adopted by FDA for OTC drug products in § 201.61 (21 CFR 201.61). These regulations relate to labeling information concerning the identity of ingredients, directions for use, and general and specific warnings. The Panel has considered these regulations and concludes that, in general, these requirements are appropriate for OTC contraceptive drug products. The term "labeling," as used by the Panel, should be understood to refer to any language developed for the consumer and placed upon the carton, the container, and package inserts. Any special labeling which the Panel believes to be indicated for a particular ingredient will be discussed under that ingredient.

According to its mandate, the Panel reviewed and classified all of the terms on product labels submitted to it. Those terms classified in Category I are appropriate and may continue to be used. Terms in Category II are vague,

poorly defined, or apt to promote impressions of unproven effectiveness. The Panel believed that the claims placed in Category III could be proven by scientific methods, but adequate data were not submitted to allow their approval as Category I claims. Any manufacturer who wishes to perform the necessary research to substantiate such claims may do so and submit the results to the FDA for approval.

The Panel believes that false, misleading, and unproven claims of vaginal contraceptive effectiveness should be prohibited during the interim period from the completion of the Panel's report to the agency's adoption of the monograph. To achieve this, the Panel recommends that FDA implement a review process for the evaluation of new or substantially modified labeling claims for vaginal contraceptive drug products.

After careful consideration of all labeling of OTC contraceptive drug products submitted, the Panel recommends the following general labeling guidelines:

1. *Indications for use.* The indications for use should be simply and concisely stated. They should enable the consumer to have a clear understanding of the results which can be anticipated from the use of the product. Any statement regarding the indications for use should be very specific and should be confined to the conditions for which the product is being recommended. A vaginal product may not be promoted for additional indications for use on other areas of the body unless there are sufficient valid data to support such claims.

2. *Ingredients.* The Panel concludes that it is important for the consumer to know all of the ingredients in a product because of the possibility of allergic states and idiosyncracies. For example, although aromatic compounds such as perfumes have no pharmacologic activity in vaginal drug products, these agents should be listed on the label because of their potential to sensitize. Although the Panel recognizes that current statutes require that only the active ingredients be listed, it strongly recommends that all inactive ingredients (including those which are necessary for formulation and product identification) also be listed, preferably with a statement of their quantity in metric units. The Panel further concludes that no product should be promoted on the basis of its inactive ingredients, nor should the label create a false impression of value beyond that which is scientifically valid.

3. *Principal display panel.* The Panel is aware of the current regulations

regarding the principal display panel, statement of identity, and the declaration of net quantity of contents for OTC drugs and concurs with those requirements (21 CFR 201.60, 201.61, and 201.62).

4. *Effectiveness and claimed advantages.* The Panel has reviewed the claims made by the manufacturers of the various products under its purview. It concludes that certain claims for effectiveness have been made in the past without valid supporting data. Therefore, any language which promises specific health benefits which are unsubstantiated by the scientific information submitted is unacceptable and may not be used to promote the sale of these products. For example, manufacturers may not make use-effectiveness or comparative-effectiveness claims such as "better than" or "the most" unless valid scientific data have been provided upon which to base such claims. Further details on specific claims will be included in the appropriate sections of this document. In general, no claims can be made which are not specifically approved by the Panel as set forth in this document.

5. *Directions for use.* The label should consist of a clear statement of the usual effective dose. When a drug is known to have a somewhat higher than average incidence of hypersensitivity reactions, an additional warning stating this fact should be included on the label.

H. Combination Policy

The Panel has noted the regulation (21 CFR 330.10(a)(4)(iv)), which states:

An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

The Panel has observed that a number of the vaginal preparations under its review contain multiple ingredients. However, the Panel concludes that, in general, the fewer ingredients in a combination product, the safer and more rational the therapy. It further concludes that consumers should be exposed to the fewest possible ingredients and at the lowest possible dosage consistent with a satisfactory level of effectiveness. Thus, in general, OTC products containing a single, safe and effective active ingredient are to be preferred over those

having multiple active ingredients. Such an approach is totally in accord with established medical principles and will reduce the risks of toxic, allergic, or idiosyncratic reactions, as well as the possibility of unrecognized or undesirable drug interactions. The Panel concludes that OTC combination drugs should contain only those inactive ingredients which are absolutely essential for pharmaceutical necessity and/or product identification. As previously stated, the Panel believes that a listing of these inactive ingredients and the quantities present should be included in the product labeling. (See part II. paragraph G. above—Labeling.)

The Panel concludes that combination vaginal contraceptive drug products will only be permitted if well-controlled laboratory and clinical trials demonstrate that each of the ingredients is not only safe but also makes a clear and specific contribution to the claimed effectiveness of the product.

(1.) *Category I contraceptive combinations.* With regard to the contraceptive products currently under its review, the Panel finds that there are no submissions which combine two or more Category I ingredients. If a manufacturer combines two or more Category I ingredients, the specific ingredients as well as the combination product must be subjected to laboratory and clinical testing using the recommended testing guidelines outlines elsewhere in this document. (See part III. paragraph G. below—Testing Guidelines for Contraceptive Effectiveness).

2. *Category II contraceptive combinations.* The Panel further concludes that any combination contraceptive drug formulation currently on the market which contains a Category II ingredient is to be placed in Category II. The following marketed combination formulations were reviewed by the Panel. In all cases the formulations contain at least one Category II ingredient. It is this factor that has led the Panel to conclude that these combinations are unsafe for OTC use or any use.

a. Phenylmercuric acetate and boric acid.

b. Phenylmercuric acetate, boric acid, and nonoxynol 9.

c. Phenylmercuric acetate, octoxynol 9, and sodium borate.

3. *Category III contraceptive combinations.* The Panel concludes that the marketed combination formulation containing methoxypolyoxyethylene glycol 550 laurate and nonoxynol 9 is safe for OTC use. However, insufficient data were presented to show that both

surfactants make a contribution to the claimed effectiveness.

III. Vaginal Contraceptive Drug Products

A. General Discussion

1. *Contraception.* The Panel concludes that contraception is an extremely important part of general health care. It further concludes that all of the current family planning modalities, both OTC and prescription, have an essential role to play in the total contraceptive armamentarium. Thus the Panel considers that the methods of vaginal contraception under its review are important and should, insofar as possible, continue to be made available to the consumer. Nevertheless, the Panel believes that an individual consumer should consult with her physician if she is have difficulty in deciding whether or not an OTC contraceptive method is appropriate for her.

A vaginal contraceptive may be defined as a drug product which is placed in the vagina prior to intercourse for the purpose of preventing pregnancy. Such contraceptives are currently available in several different forms, e.g., jellies, creams, foams, suppositories, and foaming tablets. They are all designed to protect against pregnancy in two ways: To create a physical barrier to the entrance of spermatozoa through the cervical os into the uterus and tubes, and to provide a direct spermicidal or sperm-immobilizing action.

The Panel concurs with the criteria presented in McConnell's paper dealing with spermicidal activity (Ref. 1). These criteria are as follows. First, a spermicide must act rapidly and effectively, killing all sperm on contact, or it must render the sperm incapable of fertilization; second, it must be systemically nontoxic and nonirritating to the vaginal and penile mucosa; third, it must not have an effect on the development of the embryo or fetus; and fourth, it must be free of adverse long-term toxicity.

2. *Contraceptive effectiveness.* As stated earlier in this document, the Panel recognizes that many of the studies of safety and effectiveness contained in the submissions of data and information were carried out a number of years ago. (See part II. paragraph B. above—Data Search.) As a result, the data on effectiveness and use-effectiveness are limited and conspicuously lacking in internal consistency. Little information is available on many of the ingredients except for experience gained by common practice. Unfortunately, such information does not lend itself to scientific analysis.

Valid comparisons of method-effectiveness rates for vaginal contraceptives and other agents such as oral contraceptives or intrauterine devices (IUD) cannot be made at the present time. No well-controlled studies have been carried out using patients of similar backgrounds who receive their family planning care at the same time and in the same place. Without such studies, comparisons cannot be made with statistical validity either now or, in all probability, at any time in the future.

Similarly there are no data which would allow valid comparisons of the use-effectiveness of the various vaginal contraceptive drug products. It is also unlikely that such data will be forthcoming in the future. The low frequency of use of any individual product would preclude the acquiring of statistically valid comparative data (Ref. 2). However, it may well be feasible to develop use-effectiveness data on the various classes of vaginal contraceptive products, e.g., foams, creams, foaming tablets, etc. (See part III. paragraph G. below—Testing Guidelines for Contraceptive Effectiveness.) There is fragmentary evidence available at the present time that suggests that foam preparations are somewhat more effective than the others, probably because the use of an aerosol delivery system allows for better placement of the barrier (Refs. 3 through 6).

The Panel is particularly concerned about the lack of data regarding the contraceptive effectiveness of the vaginal suppositories. Multiple factors such as proper placement, the time required for melting to release the active ingredient, and the duration of effectiveness have not been sufficiently well-documented.

3. *Surfactants as contraceptives.* Since their first recognition as spermicides 40 years ago, many surfactants (surface-active agents) have been tested for their contraceptive effectiveness. Of the three categories, ionic, nonionic, and cationic, the nonionic surfactants have been found to be the most useful in human contraception. These nonionic surfactants are the only vaginal contraceptive ingredients discussed in this document (with the exception of the mercury-containing compounds). Mann (Ref. 7) states that there is evidence to show that surfactants act directly on the constituents of the lipid-containing layer which protects the surface of the spermatozoa, producing a loss of motility and fructolytic power and a grossly altered permeability. Since the activity of sperm depends on the metabolism of fructose, the blocking of

this process effectively destroys the capacity of the organism to survive. Harvey and Stuckey showed that the surface-tension-lowering properties of the surfactants enhance their spermicidal activity (Ref. 8).

In its review of the effectiveness of vaginal contraceptive ingredients, the Panel identified several in vitro assays which have been used in the past to demonstrate the spermicidal activity of an ingredient or product. These tests, which have been reviewed by McConnell (Ref. 1), each stress different criteria. Although all of them involve the combining of sperm and spermicide, the combination is examined for different effects, e.g., the death or immobility of sperm.

In the Brown-Gamble test small amounts of sperm are mixed with dilutions of the spermicides, and the survival time of the sperm is noted. The Sander-Cramer method, which uses 0.2 mL of semen and 1.0 mL of diluted contraceptive, determines the greatest dilution of spermicide that can kill sperm instantaneously. In one of Baker's several tests, the relative effectiveness of spermicides is measured by checking the motility of the sperm at 5 and 30 minutes after 0.3 mL of sperm has been placed in various dilutions of spermicides in equal volume. Mende and Berliner devised a saturation or titration test which measures the total spermicidal power of a contraceptive. In this test, a known amount of semen, 0.1 mL, is added to 0.05 mL of spermicide, thoroughly mixed, and examined at 20 seconds. If all of the sperm are dead, an additional 0.1 mL of sperm is added, and the procedure is repeated until a sample finally shows live sperm. The International Planned Parenthood Federation Agreed Test for Total Spermicidal Power (IPPF Agreed Test) combines the principal features of Baker's tests with those of Sander and Cramer. In this test 1 mL of a spermicidal solution (diluted with 0.9-percent saline to 1 g in 11 mL) is mixed with 0.2 mL of semen. This test is used to determine at what point total sperm immobilization is accomplished.

In addition to in vitro spermicidal assays, some laboratories have recently begun to use in vivo animal models to gain information on the vaginal contraceptive potencies of experimental formulations or products (Refs. 9 and 10). Up until the present time this approach has involved the use of the rabbit and the stump-tailed macaque (*Macacca arctoides*).

A number of investigators have extended the assessment of spermicidal activity of contraceptive formulations to more closely resemble in vivo human

conditions (Refs. 11 and 12). In one such approach human volunteers use a contraceptive prior to artificial insemination. Samples are then recovered from the vaginal vault, mid vagina, and lower vagina at various times after insemination to assess the ability of the contraceptive product to immobilize sperm (Ref. 11).

Human postcoital testing (Sims-Huhner) involves intravaginal administration of a contraceptive product immediately before intercourse, followed by an evaluation of sperm motility in cervical mucus (Ref. 12). Obviously, the most convincing line of evidence for vaginal contraceptive effectiveness of an ingredient is a controlled clinical study of the pregnancy rate expressed as the percent of pregnancies which occur in 100 woman-years of use. This rate may be compared with the pregnancy rate in a similar group of women who are using no contraceptive method.

For every nonionic surfactant, the Panel has reviewed the data supporting the claimed spermicidal potency and contraceptive effectiveness. The in vitro spermidical and in vivo animal contraceptive data which the Panel reviewed were evaluated as to whether or not they supported the spermicidal or contraceptive activity of the ingredient. The spermicidal potency and ED_{50} values are reported under each Category I ingredient. Variations in these values for a single ingredient in a variety of products reflect the effect of the vehicle on the biological activity of the spermicidal ingredient.

In the submissions of data and information there is adequate testing to demonstrate that menfegol, nonoxynol 9, and octoxynol 9 effectively immobilize sperm within the acceptable time limits of various in vitro tests, e.g., Brown-Gamble, Sander-Cramer, Diffusion, and IPPF Agreed Test procedures (Refs. 13 through 19). Additionally, the long marketing history for products containing these ingredients supports the in vitro data demonstrating that these ingredients are effective.

Animal safety testing and accumulated use-experience over the past 20 years indicate an absence of local reactions of any significance. Although there are few reports in the literature up to this time, studies by Poland (Ref. 20) have demonstrated no adverse effects on the embryo from the use of these nonionic surfactants. With respect to long-term toxicity studies, the Panel finds no long-term adverse effects in any of the submissions of data, nor in the general experience with the use of these surfactants in foods, medications, and cosmetics. The Panel, therefore,

concludes that menfegol, nonoxynol 9, and octoxynol 9 are safe and effective vaginal contraceptives for OTC use. Specific ingredient reviews serve to confirm this conclusion. (See part III, paragraph B.1. below—Category I conditions under which vaginal contraceptive ingredients are generally recognized as safe and effective and are not misbranded.)

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B. Category I Vaginal Contraceptive Ingredients

1. *Category I conditions under which vaginal contraceptive ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the Federal Register.

2. *Category I active ingredients.* The Panel has classified the following vaginal contraceptive active ingredients (nonionic surfactants) as safe and effective and not misbranded:

Menfegol
Nonoxynol 9
Octoxynol 9

a. *Menfegol.* The Panel concludes that menfegol (a nonionic surfactant) is safe and effective for OTC use as a vaginal contraceptive as specified in the dosage section below.

(1) *Safety.* Menfegol has undergone extensive toxicity testing. The Panel reviewed numerous acute, subacute, and chronic toxicity studies conducted in mice, rats, rabbits, and dogs which substantiated the safety of this ingredient. These were conducted using the intravenous, subcutaneous, oral, and vaginal routes of administration. In one 3-month study on rats, no adverse effects were indicated when menfegol was administered intravaginally at 12.5 or 50 milligrams per kilogram of body weight (mg/kg). In a 6-month chronic toxicity study, no drug-related adverse effects were indicated in the female rats which were injected subcutaneously with menfegol at dose level of 0.3, 3.0, and 30 mg/kg. Histopathologic examination revealed no organ abnormalities in the 0.3 and 3.0 mg/kg group; the only change in the 30.0 mg/kg group was slight liver congestion (Ref. 1).

Teratology studies using pregnant rats and mice demonstrated no adverse effects of menfegol on either fetuses or newborn animals at sublethal parenteral doses (Ref. 1). This ingredient has an oral LD_{50} of 8,000 mg/kg in mice.

The Panel reviewed seven clinical studies which recorded the frequency and nature of side effects associated with the use of menfegol (Ref. 2). For example, data from one study of 1,164 women indicated the most common side effects to be a sensation of warmth (16 percent) and slight vaginal discharge (16 percent). The Panel noted that vaginal absorption of menfegol has not yet been studied in the human. However, because of its extensive animal safety testing, its 10-year marketing history in several foreign countries without report of serious adverse reaction (Ref. 2), and its

close chemical similarity to the other nonionic surfactants under review, the Panel concludes that menfegol is safe for OTC use.

(2) *Effectiveness.* Menfegol is a highly spermicidal nonionic surfactant. In vitro and clinical studies presented to the Panel indicate high degrees of use-effectiveness (Ref. 1). The Panel reviewed seven human effectiveness tests conducted for 12 to 18 months. The pregnancy rates in these studies ranged from 2.3 to 7.7/100 woman-years (Pearl Index basis). Postcoital testing of a product containing only menfegol as the spermicidal agent showed no spermatozoa in the cervical mucus of most patients. When spermatozoa were found, their motility was very low.

Menfegol contained in a foaming tablet formulation produced a dose-dependent decrease in the implantation rate when the tablet was placed in the vaginas of rabbits prior to mating. The vaginal contraceptive potency of menfegol in this dosage form— expressed as that dose which reduced the implantation rate to 50 percent that of the control series (ED_{50})—was 53 mg of product, corresponding to 4.0 mg of ingredient. Using the Sander-Cramer method of testing for sperm immobilization, 0.38 mg/mL of menfegol immobilized all sperm within 20 seconds (Ref. 1). The Panel concludes that menfegol is an effective contraceptive for OTC use.

(3) *Dosage.* A single dose of the product must deliver the active ingredient in concentrations which as a minimum meet those standards of acceptability set forth in the effectiveness-testing section of this document. (See part III. paragraph G.1. below—Testing Guidelines for Contraceptive Effectiveness.)

(4) *Labeling.* The Panel recommends the Category I labeling for contraceptive ingredients. (See part III. paragraph B.3. below—Category I labeling for vaginal contraceptive drug products.)

(5) *Directions.* The amount of the formulation to be used and the optimum time prior to intercourse at which the spermicide should be used varies with the formulation. Specific directions for use will be determined from the data derived from the required testing for each product. The directions must clearly indicate the amount of the product to be placed in the vagina and how long prior to intercourse this must be done in order to produce effective contraception. Additionally the period of time during which the product can be expected to retain its effectiveness must be stated. Other nonspecific labeling is outlined elsewhere in this document. (See part II. paragraph G.5. above—

Directions for use and part III. paragraph B.3. below—Category I labeling for vaginal contraceptive drug products.)

References

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(2) OTC Volume 110040.

b. *Nonoxynol 9.* The Panel concludes that nonoxynol 9 (a nonionic surfactant) is safe and effective for OTC use as a vaginal contraceptive as specified in the dosage section below.

(1) *Safety.* The Panel reviewed several animal toxicity studies all of which substantiate the safety of this ingredient. Data submitted by one manufacturer (Ref. 1) reported that the oral LD_{50} in rats was 2.59 mL/kg. The single skin application LD_{50} in rabbits was 2.83 mL/kg. Following a single application of 0.01 mL of the pure ingredient to the uncovered skin of rabbits, primary skin irritation was slight when examined after 24 hours. When instilled in rabbit eyes, a 10 percent solution of the ingredient in water caused definite eye injury described in the submission as "surface damage."

Smyth and Calandra (Ref. 2) investigated the toxicology of an extensive series of alkylphenol polyoxyethlene nonionic surfactants. Included in this study were three different commercial samples of nonoxynol 9 as well as octoxynol 9 which is discussed below. These investigators determined that the oral LD_{50} of nonoxynol 9 in male rats was 2.6 mL/kg. Feeding nonoxynol 9 to rats for 90 days at doses of 0.01, 0.05, 0.25, and 1.25 g/kg/day resulted in decreased food intake among females at all dose levels. The 0.25 g/kg/day dose level resulted in decreased weight gain in both males and females and increased liver to body weight ratios. Slight histopathological changes in the kidney and liver were seen at this dosage level. In a similar experiment rats were fed diets containing 0, 0.01, 0.04, 0.16, 0.64, 2.5 and 5.0 percent nonoxynol 9. No histopatholgical changes were seen. Emaciation and poor organ development in rats consuming the two highest dietary concentrations were attributed to poor palatability of the food. In a third 90-day feeding study, rats were fed nonoxynol 9 at 0, 0.1, 0.3, and 1.0 percent of the diet. The 0.1 percent dose level caused no effect, whereas the 1.0 percent level resulted in decreased growth. Slight histopathological changes were seen in the liver, kidney, and spleen of rats given the two higher doses, but the authors considered these to be of no toxicological significance.

When nonoxynol 9 was fed to beagle dogs at levels of 0.04, 0.64, and 5.0

percent for 90 days, using one dog per dose level, no histopathologic changes were seen either in the treated group or the three untreated control dogs.

Nonoxynol 9 was also administered in the diet of rats at levels of 0.03, 0.09, and 0.27 percent for 2 years. There were no differences noted between control and treated rats in any observations made (e.g., food consumption, mortality, extraneous infections, liver and kidney to body weight ratios, body weight ratios, body weigh gain, red blood cell count, incidence and location of neoplasm, and histopathologic lesions). A similar study in which the same levels were fed to beagle dogs for 2 years also showed no effect other than an increased liver to body weight ratio in the dogs which consumed the 0.27-percent diet. Microscopically the livers of these dogs appeared to be normal.

Olson and coworkers (Ref. 3) studies the acute toxicity of nonoxynol 9 along with a number of other surfactants. They calculated an oral LD_{50} in rats of approximately 1.6 g/kg. A 1-percent aqueous solution of nonoxynol 9 instilled in the eye of rabbits resulted in very slight conjunctivitis, whereas a 5-percent solution caused moderate corneal injury. When aqueous solutions of nonoxynol 9 (1, 5, and 25 percent) were applied to the uncovered intact skin of rabbits, even the most concentrated solution resulted in only slight erythema (redness of the skin) demonstrating a low potential for irritation.

In another study (Ref. 1) four female dogs were treated intravaginally with 5 cc of a 12.5-percent solution of nonoxynol 9 in aerosol foam twice daily each weekday and once each day on Saturdays and Sundays for 6 months. This represents a dose that is about 10 times greater on a per kilogram basis than the recommended human dose. Two control dogs were treated intravaginally with 5 cc of normal saline solution on an identical schedule. Hematological examination, urinalysis, and clinical chemistry showed no outstanding differences between treated and control animals. No changes were seen in behavior, food consumption, or weight gain in the animals treated with nonoxynol 9. Half the treated dogs had acute ulcerative vaginitis which the authors attributed to the frequency and relatively large volume of administration. One of the two control dogs displayed a slight low-grade acute vaginitis which was attributed to similar causes.

Excretion studies by Knaak, Eldrige, and Sullivan (Ref. 4) in which a single 10-mg dose of radiolabeled nonoxynol 9 was administered orally to rats

indicated that over 90 percent of the administered dose was eliminated within 2 days after administration.

Based on these data and the lack of reports of significant adverse effects in humans using products containing nonoxynol 9, the Panel concludes that nonoxynol 9 is safe for OTC use.

(2) *Effectiveness.* The effectiveness of nonoxynol 9 (a nonionic surfactant) has been well-established over more than 20 years of use (Ref. 3). In vitro laboratory tests and in vivo animal experiments cited in the surfactant discussion above have demonstrated the spermicidal activity of this class of compounds. (See part III. paragraph A.3. above— Surfactants as contraceptives.)

Using the Sander-Cramer sperm immobilization method of testing, 0.12 mg/mL immobilized all spermatozoa within 20 seconds (Ref. 5). Using the Mende and Berliner saturation or titration test, 320 mL of human semen were immobilized by 1 g of foam formulation containing nonoxynol 9, while 1 g of cream formulation containing the ingredient immobilized 105 mL of human semen (Ref. 5).

Nonoxynol 9 contained in an aerosol foam (12.0 percent), melting suppository (2.0 percent), foaming suppository (2.5 percent), and cream formulations (5.0 percent) produces dose-dependent decreases in the implantation rates in rabbits when placed in the vaginas prior to mating. Vaginal contraceptive potencies—expressed as that dose of product which reduces implantation rate to 50 percent that of the control series (ED_{50})—were 2.3 mg, 120 mg, 149 mg, and 390 mg of aerosol foam, melting suppository, foaming suppository, and cream formulation, respectively (Refs. 6, 7, and 8). Postcoital testing showed no spermatozoa in cervical mucus in most of the patients. Where spermatozoa were found, their motility was very low (Ref. 5).

In 6 clinical studies involving a total of 425 patients who used a cream formulation containing nonoxynol 9 for a total of 4,071 months, the pregnancy rates (i.e., the percent of pregnancies which occur in 100 woman-years of use) were 2.1 percent for "correct use" and 3.5 percent for "incorrect or irregular use" (Ref. 1). In other studies involving a total of 995 patients who use a foam formulation containing nonoxynol 9 for a total of 4,634 months, the pregnancy rates ranged from 2.2 to 2.4 percent for "correct use" and 3.7 to 5.4 percent for "incorrect or irregular use" (Ref. 1).

The Panel concludes that nonoxynol 9 is an effective contraceptive for OTC use.

(3) *Dosage.* A single dose of the product must deliver the active

ingredient in concentrations which as a minimum meet those standards of acceptability set forth in the effectiveness-testing section of this document. (See part III. paragraph G.1. below—Testing Guidelines for Contraceptive Effectiveness).

(4) *Labeling.* The Panel recommends the Category I labeling for contraceptive ingredients. (See part III. paragraph B.3. below—Category I labeling for vaginal contraceptive drug products.)

(5) *Directions.* The amount of the formulation to be used and the optimum time prior to intercourse at which the spermicide should be used varies with the formulation. Specific directions for use will be determined from the data derived from the required testing for each product. The directions must clearly indicate the amount of product to be placed in the vagina and how long prior to intercourse this must be done in order to produce effective contraception. Additionally, the period of time during which the product can be expected to retain its effectiveness must be stated. Other nonspecific labeling is outlined elsewhere in this document. (See part II. paragraph G.5. above—Directions for use and part III. paragraph B.3. below— Category I labeling for vaginal contraceptive drug products.)

References

(1) OTC Volume 110005.
(2) Smyth, H. F., and J. C. Calandra, "Toxicologic Studies of Alkylphenol Polyethylene Surfactants," *Toxicology and Applied Pharmacology*, 14:315–334, 1969.
(3) Olson, K. J., et al., "Toxicological Properties of Several Commercially Available Surfactants," *Society of Cosmetic Chemists Journal*, 13:469–476, 1962.
(4) Knaak, J. B., J. M. Eldridge, and L. J. Sullivan, "Excretion of Certain Polyethylene Glycol Ether Adducts of Nonylphenol by the Rat," *Toxicology and Applied Pharmacology*, 9:331–340, 1966.
(5) OTC Volume 11036.
(6) Homm, R. E., et al., "Relative Antifertility Activity of Three Vaginal Contraceptive Products in the Rabbit: Relationship to In Vitro Data," *Contraception*, 13:4, April 1976.
(7) Homm, R. E. et al., "A Comparison of the In Vivo Contraceptive Potencies of a Variety of Marketed Vaginal Contraceptive Dosage Forms," *Current Therapeutic Research*, 22:588–595, 1977.
(8) Greenslade, F.C., et al., "The Rabbit as an In Vivo Animal Model for the Study of Vaginal Contraceptive Potency," *in* "Risks, Benefits, and Controversies in Fertility Control," Edited by Sciarra, J. J., et al., Harper and Row, Hagerstown, MD, pp. 534–546, 1978.

c. *Octoxynol 9.* The Panel concludes that oxtoxynol 9 (a nonionic surfactant) is safe and effective for OTC use as a

vaginal contraceptive as specified in the dosage section below.

(1) *Safety.* Octoxynol 9, like nonoxynol 9, is an alkylphenol polyoxyethylene nonionic surfactant. It is identical to nonoxynol 9 in chemical structure except that the alkyl group which substitutes the phenol portion of the molecule is a diisobutyl group rather than a straight chain nonyl group. This difference has no significant effect on the biological and chemical properties of the compound, a fact that is illustrated by the review of toxicity data on this class of nonionic surfactants by Smyth and Calandra (Ref. 1). Moreover, testing of a commercial product containing octoxynol 9 by intravaginal administration to female rabbits and monkeys resulted only in mild vaginal irritation (Ref. 2). On the basis of its similarity to nonoxynol 9 and a 20-year marketing experience which has elicited no safety problems, the Panel concludes that octoxynol 9 is safe for OTC use.

(2) *Effectiveness.* In one study using the Sander-Cramer sperm immobilization method, 0.24 mg/mL of octoxynol 9 immobilized all spermatozoa within 20 seconds (Ref. 2). Using the Mende and Berliner saturation or titration test, 13 mL of human semen were immobilized by 1 g of gel formulation. Octoxynol 9 contained in a 3-percent cream and in a 1-percent gel formulation produced dose-dependent decreases in the implanation rate in rabbits when placed in the vagina prior to mating. Vaginal contraceptive potencies—expressed as that dose of product which reduces the implanation rate to 50 percent that of the control series (ED_{50})—were 1,400 mg and 2,800 mg for cream and gel, respectively (Refs. 3, 4, and 5).

In clinical studies involving a total of 485 patients who used a gel formulation containing octoxynol 9 for a total of 3,728 months, the pregnancy rates (i.e., the percent of pregnancies which occur in 100 woman-years of use) were 3.3 percent for "correct use" and 4.7 percent for "incorrect or irregular use" (Ref. 2).

(3) *Dosage.* A single dose of the product must deliver the active ingredient in concentrations which as a minimum meet those standards of acceptability set forth in the effectiveness testing section of this document. (See part III. paragraph G.1. below—Testing Guidelines for Contraceptive Effectiveness.)

(4) *Labeling.* The Panel recommends the Category I labeling for vaginal contraceptive ingredients. (See part III. paragraph B.3 below—Category I labeling for vaginal contraceptive drug products.)

(5) *Directions.* The amount of the formulation to be used and the optimum time prior to intercourse at which the spermicide should be used varies with the formulation. Specific directions for use will be determined from the data derived from the required testing for each product. The directions must clearly indicate the amount of the product to be placed in the vagina and how long prior to intercourse this must be done in order to produce effective contraception. Additionally, the period of time during which the product can be expected to retain its effectiveness must be stated. Other nonspecific labeling is outlined elsewhere in this document. (See part II. paragraph G.5. above—Directions for use and part III. paragraph B.3. below—Category I labeling for vaginal contraceptive drug products.)

References

(1) Smyth, H. F., and J. C. Calandra, "Toxicologic Studies of Alkylphenol Polyethylene Surfactants," *Toxicology and Applied Pharmacology*, 14:315–334, 1969.
(2) OTC Volume 110005.
(3) Homm, R. E., et al., "Relative Antifertility Activity of Three Vaginal Contraceptive Products in the Rabbit: Relationship to In Vitro Data," *Contraception*, 13:4, 1976.
(4) Homm, R. E., et al., "A Comparison of the In Vivo Contraceptive Potencies of a Variety of Marketed Vaginal Contraceptive Dosage Forms," *Current Therapeutic Research*, 22:588–595, 1977.
(5) Greenslade, F. C., et al., "The Rabbit as an In Vivo Animal Model for the Study of Vaginal Contraceptive Potency," *in* "Risks, Benefits, and Controversies in Fertility Control," Edited by Sciarra, J. J., et al., Harper and Row, Hagerstown, MD, pp. 534–546, 1978.

3. *Category I labeling for vaginal contraceptive drug products.* As the Panel continued its review, it became increasingly aware of the major importance of vaginal contraception as a method within the total contraceptive armamentarium. This awareness paralleled the growing concern about immediate and possible long range side effects of other methods of fertility control. Since vaginal contraceptives are available without prescription and are frequently used without professional advice or guidance, it is all the more important that their labeling be as informative and as explicit as possible in order to promote the effective use of these products by the consumer.

The Panel recognizes that the effectiveness of any vaginal contraceptive ingredient is directly related to the accuracy and consistency with which the product containing this ingredient is used. Consequently, the Panel recommends that the concepts

embodied in the terms "method-effectiveness" and "use-effectiveness," as previously defined in this document, be conveyed to consumers. (See part II. paragraph A. above—General Discussion, Introduction.) The required information should be included in a package insert or any other appropriate labeling. This information should be presented in language which can be easily read, easily understood, and readily retained by the consumer. "Method-effectiveness" should be described as that level of effectiveness which is attained by women who follow the manufacturer's instructions exactly and use the product every time they have sexual intercourse. "Use-effectiveness" should be described as that level of effectiveness which is attained by a large group of women some of whom either fail to use the product correctly or do not use it each time they have sexual intercourse.

The Panel concludes that in order for women to obtain the maximum protection against unwanted pregnancy it is essential that directions for the use of vaginal contraceptive products be accurately followed. It, therefore, believes that the directions for use should be clearly stated and illustrated in order to provide easily understandable guidance to the consumer.

Since some women douche following coitus, concern has been expressed that douching not follow intercourse too closely when a vaginal contraceptive is used in order to allow the spermicide time for effective action (Ref. 1). There are no data that document the optimum time interval that douching should be delayed. Historically, however, the generally accepted opinion holds that when vaginal contraceptives are used as the primary method of birth control, douching should be delayed for at least 6 hours after coitus. This fact should be included in the information given to the consumer.

Because a variety of dosage forms are used in the application of vaginal contraceptives (gels, creams, aerosol foams, effervescent or melting suppositories, etc.), the Panel has not attempted to provide wording and directions for each product. It recommends that proper instructions for use be the responsibility of the manufacturer and that they conform to the following general guidelines.

a. *Principal display panel.* In addition to any promotional material for a vaginal contraceptive product, the Panel believes that the principal display panel should contain certain information which is important for the correct use of the product by the consumer. While

impairment may become manifest in school-age children.

The apparent problems in surveillance and the difficulties in recognizing a causal relationship between birth defects and chemical agents have been further elucidated by experimental studies (see below) on animals treated with PMA. In brief, it was demonstrated that PMA is readily absorbed from the vagina—this has also been reported for the human vagina (Ref. 7). After absorption, PMA and its Metabolic product, Inorganic mercuric ion (Hg^{++}), are distributed in various tissues of the fetal compartment. Moreover, mercury compounds are excreted in milk. Most importantly, PMA is embryotoxic; PMA and Hg^{++} adversely affect critical biochemical systems in the cells of most tissues, particularly the nervous system. These processes are briefly discussed below.

(ii) *Biochemistry of mercury compounds.* An understanding of the biochemical mechanisms underlying the toxic action of PMA in animals provides the theoretical basis for the extrapolation from animals to man. Mercurial compounds are highly reactive, nonspecific enzyme inhibitors and membrane poisons (Ref. 15).

These actions may be ascribed to the high binding affinity of all ionic forms of mercury for the thiol or sulfhydryl ($-SH$) group of the amino acid cysteine, and for the thiol groups in proteins containing one or more residues of cysteine. PMA dissociates to furnish the organic mercuric ion ($C_6H_5Hg^+$). PMA is also readily metabolized to yield inorganic mercuric ion (Hg^{++}). For instance, the dissociation constant for the interaction of Hg^{++} with cysteine is of the order of 10^{-20} molar; the negative logarithm of the dissociation constant (i.e., the pK value) is 20.1. The pK values for the interaction of CH_3Hg^+ with cysteine and serum albumin are 15.7 and 22, respectively (Ref. 16). Although $-SH$ groups are the primary site of mercurial binding, other functional groups in amino acids interact with mercurial ions. Van der Linden and Beers (Ref. 17) studied complex formation between Hg^{++} and all of the 20 amino acids that are important in protein synthesis. Chelation takes place by the *alpha-* amino-carboxylate group (R-CNH_2- COO-). In the case of histidine, complex formation takes place mainly through the nitrogen atom in the imidazole ring and the *alpha-*amino group. The ligand-binding action of mercurial compounds interfers with the function of plasma and intracellular membranes, thus suppressing erythrocyte potassium (K^+) permeability, glucose-uptake in the

excised rat diaphragm, mitochondrial oxidative phosphorylation and K^+ binding, and mitochondrial swelling (Ref. 18). These authors studied the effect of Hg^{++} and PMA on hepatic lysosomal membrane integrity. An irreversible loss of structure-linked latency occurred with resulting enzyme activation. The lysosomal hydrolases studied were phosphohydrolase, *beta-* glucuronidase, and *n*-acteyl-*beta*-D-glucosaminidase.

Southard, Nitisewojo, and Green (Ref. 19) elucidated mechanisms in the perturbation of the mitochondrial control system by mercurial compounds. Oxidative phosphorylation, calcium transport, and phosphate accumulation are suppressed by mercurial compounds; whereas adenosine triphosphate (ATP) hydrolysis, K^+ transport, magnesium (Mg^{++}) transport, and configurational change are induced. The endogenous mitochondrial ion transport mechanisms are perturbed as a result of an alteration in a few critically located sulfhydryl groups contained within proteins that are intrinsic to the inner mitochondrial membrane. The accumulation of mercury in mitochondria (e.g., in the kidney of rats exposed to a lethal dose of mercuric chloride) alters the functional capabilities and ultrastructure of the mitochondria, suppreses oxidative phosphorylation, and results ultimately in the death of the animal. The properties of a mercurial-dependent ATPase activity have been examined also in isolated beef-heart mitochondria (Ref. 20).

Biochemical mechanisms underlying the neurotoxic effects of mercurial compounds have been investigated by Chang, Desnoyers, and Hartmann (Ref. 21). Adult male rats were intoxicated with methylmercuric chloride (CH_3HgCl) or mercuric chloride ($HgCl_2$). Single neurons were dissected from the dorsal root ganglia. The ribonucleic acid (RNA) of these neurons was extraced, and the base composition of the RNA analyzed. Short-term exposure to the mercurial compounds resulted in a reduction of the total RNA in these neurons without change in the base composition. Prolonged exposure to $HgCl_2$ resulted, however, in a change in RNA base composition ratios. These results are significant since RNA plays a central role in protein systhesis by ribosomes. Other investigators (Ref. 22) reported morphological modification of the endoplasmic reticulum and the ribosomes in the nerve cells after organic mercury intoxication. The susceptibility of nerve cells to mercurial

compounds may depend upon their protein synthesizing activity.

The rate at which mercurial compounds pass through the plasma membrane of cells may be determined, in part, by the physical properties of these compounds. The unsubstituted alkyl and aryl mercury compounds are more soluble than Hg^{++} and its complexes in lipids (Ref. 15). The simple alkyl mercury compounds are about 100 times more soluble in lipids than in water. This property will presumably allow the organic mercury compounds to penetrate more readily than inorganic mercury into cells and tissues. Evidence for this is provided by the greater central nervous system toxicity of the organic mercury compounds (Ref. 15). The absorption rate of PMA from vaginal mucosa depends on the oil-water partition coefficient of the drug; the absorption rate of PMA is enhanced in the presence of the surfactant Carbowax 200 (Ref. 23). The low solubility of calomel (HgCl) and elemental mercury (Hg) in water probably accounts for the relatively low oral toxicity of these compounds.

(iii) *Acute toxicity studies on mercury compounds.* Regarding the acute toxicity (LD_{50}) for various mercury compounds, it appears that the arylmercury compound PMA is toxic like other mercury compounds, e.g., the LD_{50} values for PAM, $HgCl_2$, and ethylmercuric chloride are 8 to 37, 5 to 7, and 12 to 15 mg Hg/kg of body weight, respectively, in the mouse. However, chronic dosage with PMA was tolerated at relatively low levels in some animal experiments (Ref. 24). For instance, oral administration of phenylmercuric chloride to piglets at a level of 0.2 to 4.6 mg of mercury equivalent/kilogram/day (Hg/kg/day) for 1 to 90 days (total dose, 2.7 to 68 mg Hg/kg body weight) produced no signs of intoxication, whereas piglets which received 2.3 to 4.6 mg Hg/kg/day for 14 to 63 days (total dose, 32 to 320 mg Hg/kg/body weight) incurred histological lesions in the gastrointestinal tract, kidney, and liver in 1 to 31 days (Ref. 25).

(iv) *Maternal-fetal transfer of mercury compounds in animals.* Studies on placental passage of inorganic mercury are pertinent to a discussion of PMA because aryl mercuric compounds such as PMA are rapidly metabolized to Hg^{++} (Ref. 26).

Berlin and Ullberg (Refs. 27 and 28) studied the localization and uptake of isotopic mercury, ^{203}Hg, in pregnant mice following a single intravenous injection of isotopic PMA or $HgCl_2$ (0.5 mg Hg/kg of body weight in both instances); the stage of gestation was not stated. Autoradiography indicated a high

concentration of mercury in the placenta but only a trace in the fetus in the initial period following the injection of either mercury compound. However, after 8 to 16 days, the yolk sac epithelium and the fetal membranes showed a greater retention of mercury (after injections of PMA) than the placenta.

These observations were confirmed and extended by Suzuki et al. (Ref. 29). Isotopic $HgCl_2$ (1.5 mg Hg/kg) and PMA (2.5 mg Hg/kg) were injected subcutaneously into mice on the 14th day of gestation; the animals were sacrificed 4 days later. Radioactive mercury (^{203}Hg) in the organs and tissues was estimated by scintillation counting. The percent of administered mercury retained per fetus was 0.143 and 0.074 for $HgCl_2$ and PMA, respectively; the total amount of mercury retained per litter was proportional to the number of fetuses per litter. The mercury was distributed in the head as well as the trunk of the fetus. The concentration of mercury in the placenta and amniotic membranes was considerably higher than that of the fetus; the amniotic fluid also contained mercury. Similar experiments were performed with methylmercuric acetate; considerably more mercury, i.e., about 1.4 percent of the administered dose, was retained by the fetus.

In a more recent study by Garrett, Garrett, and Archdeacon (Ref. 30), a trace dose of isotopic $HgCl_2$ was injected intravenously into rats on the 16th day of gestation, and the animals were sacrificed 30 minutes after the injection. Isotopic mercury in tissues was estimated by scintillation counting. The concentration of ^{203}Hg was 0.023, 1.68, and 0.83 nanograms/gram (ng/g) in the fetus, chorioallantois, and yolk sac, respectively. Although the latter tissues retain much more mercury than the fetus and suggest a barrier function, it could not be concluded that the fetus is thus protected from the toxic effects of mercury.

Mansour et al. (Ref. 31) sought more information on the maternal-fetal transfer of mercury on a long-term basis, i.e., during late gestational stages and up to 3 weeks after delivery. Inorganic mercury, as $Hg(NO_3)_2$, and the highly toxic alkylmercury compounds, CH_3HgCl, radiolabeled with ^{197}Hg and ^{203}Hg, respectively, were administered subcutaneously in trace doses to rats at day 16, 18, and 20 of gestation. The concentrations of inorganic mercury in the placenta were 6 to 17 times higher than those in the newborn rat; in the case of the alkylmercury compound, the concentrations in the placenta and the pups were similar. The total body

content of inorganic mercury was 0.07 ± 0.01 and 0.14 ± 0.04 percent of the administered dose in the infant at birth and at 3 weeks of age, respectively—the dose was administered to the mother on day 12 of gestation. The corresponding values for organic mercury content were much higher, i.e., 1.16 and 0.91 percent, respectively. The concentrations of inorganic mercury in tissues and organs of the newborn rat at 3 weeks were 0.001 ± 0.001 (blood), 0.029 ± 0.013 (liver), 0.044 ± 0.011 (kidney), 0.002 ± 0.001 (brain), and 0.005 ± 0.002 (hair), calculated as a percentage of the administered dose. The authors suggested that analysis of the placenta for mercury might be used to monitor mercury levels in newborn mammals.

In two studies Shimizu (Ref. 32) examined the distribution of PMA in nonpregnant rats and then the maternal-fetal transfer of PMA in pregnant rats. In the first study, PMA-^{203}Hg tablets were inserted into the vagina at various stages of the estrous cycle. Radioactive mercury appeared in the blood within a few hours after administration of a 1-mg tablet; a maximal blood level of about 1 microgram (μg) of PMA-$^{203}Hg/0.1$ mL was attained, and began to decline about 48 hours after vaginal insertion of the tablet. When the same amount of PMA-^{203}Hg was administered in 5 divided doses over a period of 5 days, a constant blood level of about 0.2 μg PMA-$^{203}Hg/0.1$ mL was maintained for the first 5 days; it declined slowly thereafter. The stage of the estrous cycle had no effect, and similar results were obtained with hysterectomized and hysterectomized-ovariectomized rats, indicating that vaginal absorption of PMA was independent of the estrous cycle. About 33 to 55 percent of the total radioactivity administered as PMA-^{203}Hg was excreted in the urine and feces; the latter was the major route of excretion. About 6 to 15 percent of the administered radioactivity was recovered 24 hours later in the kidneys, and about 2 to 7 percent in the liver. Much smaller amounts were recovered in the brain, heart, lungs, stomach, spleen, and uterus. The brain contained about 0.15 to 0.35 μg of PMA-$^{203}Hg/g$ of tissue.

In Shimizu's second study (Ref. 32) 5-mg tablets of PMA-^{203}Hg were inserted into the vaginas of 6 rats on day 1 of pregnancy. The maternal blood levels of PMA-^{203}Hg promptly rose to a maximum of about 5 $\mu g/0.1$ mL, and declined slowly after day 2 of pregnancy. No PMA was found in the placenta or fetus on day 19 of pregnancy. No PMA was found in the 2-week-old offspring nor was there any external deformity,

change in litter size, or growth retardation. In another experiment with 4 rats, 6-mg tablets of PMA-^{203}Hg were inserted intravaginally on day 18 of pregnancy. The fetuses and placenta were removed 24 hours later. The content of PMA-^{203}Hg varied widely, from about 0.1 to 3 $\mu g/g$ and 0.4 to 12 $\mu g/g$ of fetal and placental tissue, respectively. The concentration of radioactivity in the fetus correlated with that in the placenta.

(v) *Teratogenicity of PMA and inorganic mercury.* Many years after the introduction of PMA in vaginal contraceptive preparations (Ref. 1), a systematic investigation was made regarding its possible teratogenicity as a result of continued use after contraceptive failure. Murakami, Kameyama, and Kato (Ref. 33) introduced 0.1 mg of PMA in tablet form (a contraceptive preparation) into the vaginas (S_1 group) of mice on day 7 of gestation. An aqueous solution of the same amount of the PMA tablet was injected subcutaneously in another group (S group) of mice on day 8 of gestation. Both groups of treated mice and a control group of untreated pregnant mice were sacrificed on day 14 of gestation. The number of normal embryos per litter was significantly reduced in the PMA-treated groups. The percentage of abnormal embryos was 15.1 and 9.1 percent in the S_1 and S_1 groups, respectively, and only 2.7 percent in the control group. Most of the abnormalities involved the central nervous system; histological examination indicated proliferative processes of the cellular elements of the ependymal layer (the lining membrane) throughout the medullary tube, including the brain and spinal cord. The rate of embryonic death in the treated groups was about twice that in the control group. The maternal mice in the treated groups showed evidence in many cases of acute mercury poisoning; pathological lesions were found in the liver and kidneys.

Gale and Ferm (Ref. 34) reported a systematic study of the effects of mercuric acetate and PMA on embryogenesis in the golden hamster. The mercury compounds were injected intravenously on day 8 of gestation. A sham-treated group of pregnant hamsters was used as a control. The animals were sacrificed on day 12 or 14 of gestation; the fetuses were recovered, examined, and found to exhibit a delayed growth rate and various degrees of a dorsally localized subcutaneous edema. The edematous swellings resembled the blister formations or blebs found on the heads of the mouse

fetuses in the study of Murakami, Kameyama, and Kato, discussed above (Ref. 33). The resorption rates in the hamsters were much higher than the control level of 4 percent. A small number of miscellaneous abnormalities were observed including: exencephaly, slight encephalocele, anophthalmia, microphthalmia, cleft-lip and palate, rib fusions, and syndactylia. With the exception of one instance of exencephaly, none of these abnormalities were noted in control embryos. Both mercury compounds produced signs of symptoms of toxicity in the maternal hamsters, e.g., weight loss, kidney lesions diarrhea, slight tremor, and somnolence.

(vi) *Excretion of mercury in milk.* Evidence for the mammary transmission of mercury from maternal rats to the suckling litter was obtained by Mansour et al. (Ref. 31). A trace dose of inorganic mercury, $^{203}Hg(NO_3)_2$, was injected subcutaneously into four rats 24 hours after delivery; the maternal rats and their litter were sacrificed 3 weeks later. The percentage recoveries of radioactive mercury in the tissue and organs of the rats were 0.002 ± 0.001 (whole blood), 0.056 ± 0.023 (liver), 0.083 ± 0.017 (kidney), 0.002 ± 0.001 (brain) and 0.016 ± 0.012 (hair). The recovery of mercury was much higher in the maternal rat, particularly in the kidney (10.2 ± 2.3 percent). Studies with CH_3HgCl, radiolabeled with ^{203}Hg, produced similar results; however, more radioactive mercury was recovered in the hair (i.e., 0.21 percent and 0.12 percent in maternal and newborn hair, respectively). The authors concluded that both forms of mercury, i.e., Hg $(NO_3)_2$ and CH_3HgCl, seem to be tansferred through milk to about the same extent. These findings suggest that milk could play an important role in the accumulation of mercury in nursing infants. It would seem prudent for mothers with a known history of exposure to mercury not to nurse their babies. The authors suggest also that analysis for mercury in hair samples from a newborn infant may provide an indication of the mercury burden in the infant.

The observations of Mansour et al. (Ref. 31) regarding the apparent excretion of mercury in milk are consistent with the autoradiographic studies of Berlin and Ullberg (Ref. 27), who reported an accumulation of mercury in the mammary glands of pregnant mice following a single intravenous injection of radioactive $HgCl_2$. The latter authors cited evidence obtained by other investigators for the excretion of mercury in human milk.

Evidence for the mammary transmission of mercury to the brain of suckling rats was obtained by Yang et al. (Ref. 35), who administered a single oral dose of CH_3HgCl, radiolabeled with ^{203}Hg, to maternal rats during the 16th day of lactation. In another study mercury was shown to be excreted in the milk of guinea pigs after intraperitoneal injection of CH_3HgCl, radiolabeled with ^{203}Hg (Ref. 36).

(vii) *Absorption, metabolism, tissue uptake, and distribution of PMA and inorganic mercury—(a) Absorption of the mercury compounds from the vagina.* In 1918, Macht (Ref. 37) took exception to the prevailing opinion among physicians that drugs applied to the vagina exert only a local effect and are not absorbed into the system. In the medical literature Macht found many reports of deaths after using vaginal douches and suppositories containing highly toxic substances, including $HgCl_2$ among others. Moreover, Macht obtained experimental support for his thesis using cats and dogs. He felt that dogs were especially favorable experimental animals for such studies because their vaginal mucosa is "histologically practically the same as that of the human being." He included a large variety of substances, noting both the toxicological and pharmacodynamic effects and symptoms as proof of absorption from the vagina and passage into the bloodstream. Hartman (Ref 38) emphasized the significance of these and related observations.

The introduction of PMA as a vaginal contraceptive (Ref. 1) raised questions as to the amount of mercury which may be absorbed from the vaginal tract, and whether the amount thus absorbed may be toxic. Eastman and Scott (Ref. 39) reported that about 3 to 4 percent of the mercury instilled as PMA into the human vagina was recoverable in the urine. These investigators assumed that this amount represented the total absorption. Laug and Kunze (Ref. 40) pointed out, however, that this does not indicate the amount of mercury that might have been absorbed and stored in the tissues. The latter authors demonstrated that the absorption of mercury, as reflected by its storage rather than by its excretion, can be far greater. An aqueous 0.05 percent solution of PMA was instilled into the vaginas of young female rats; in some experiments PMA was administered in a water-soluble jelly with similar results. This is the same concentration used in a commercial preparation in which PMA is dispersed in a jelly for human use (Ref. 3). The average calculated dose of mercury as PMA was $36\mu g/kg$ which is

50 percent larger than the estimated average human dose. About 25 percent of the mercury in the administered PMA was recovered in the liver and kidney following a 24-hour vaginal exposure to the drug. In view of the repeated use of PMA as a contraceptive, the authors determined the rate at which stored mercury is discharged from the liver and kidney after a single 24-hour exposure. It was observed that once the mercury entered the organism, its removal was very slow.

It may be inferred from the studies of Murakami, Kameyama, and Kato (Ref. 33), described above, that PMA is absorbed also from the vaginal of pregnant mice since teratogenic effects and pathological lesions in the liver and kidneys of the maternal mice were observed following vaginal exposure to the drug.

PMA is also rapidly absorbed from the vaginas of young, sexually mature rabbits (Ref. 23). It appears in the blood in appreciable concentration, soon after insertion of PMA-^{203}Hg as a vaginal suppository. The rate of absorption of the drug is influenced by the partition coefficient (oil/water) of the suppository vehicle (e.g., a water-soluble vehicle promotes absorption).

Of incidental interest are the comparative studies made with other mercury compounds, particularly *omega*-ethylmercurithio-*n*-undecanoic acid (EMU) which, like PMA, exhibit antitrichomonal activity. Fukuchi, et al. (Ref. 41) stated that "toxic manifestations due to the absorption of organomercurial compounds may reflect accumulation and excertion of the compounds rather than their blood level." They recorded the daily and cumulative excretions of PMA following either a single adminstration into the vagina or 30 consecutive days of vaginal administration. They also noted the tissue uptake of PMA (and EMU) following repeated daily vaginal administraion. PMA accumulated largely in the kidney and liver; small but significant amounts of PMA were detected in other tissues, including the uterus, heart, and brain.

That the blood levels of mercury increase significantly in women using vaginal suppositories containing PMA was clearly demonstrated in a study by Al-Jobori (Ref. 7). It was shown that the mean blood level of mercury rose steadily during the 3-month period when suppositories, each containing 0.4 mg PMA, were used on the average of 2 to 6 per week. In seven patients, ranging from 25 to 40 years of age, it appeared that after PMA was absorbed from the vagina, it was rapidly metabolized in part to inorganic mercury since the

increase in blood mercury wash found in both the inorganic and organic moieties. The steady increase in urinary mercury during this period was striking; about one-half of the urinary mercury was present in inorganic form. The mean blood level of urea was somewhat elevated, i.e., about 46 percent above the control level during this period. The author suggests that the increase in blood urea was due to the action of inorganc mercury, a metabolite of PMA, on the kidney. A 34-year-old patient who had been using about 3 to 4 suppositories per week for more than 12 years was also studied. The blood and urine levels of mercury appeared to be elevated. When the use of the suppositories was discontinued for 2 months, the mercury levels in blood and urine diminished significantly, and the blood urea levels decreased about 28 percent. The blood mercury levels decreased, also in another patient when she stopped using the suppositories after 3 months of usage.

(b) *Absorption of PMA from the gastrointestinal tract.* PMA is absorberd in appreciable amounts from the gastrointestinal tract of rats (Ref. 42). Mercury appeared in high concentrations in the liver and kidney and in relatively low concentrations in the brain. Tokuomi (Ref. 43) reported that a considerable amount of mercury was excreted in the urine of a person who had ingested a large amount of phenylmercury compound, representing about 1 gram of mercury. It is not clear whether any clinical symptoms were observed.

(c) *Absorption of PMA through the skin.* Clinical data reviewed by Skerfving (Ref. 24) indicate that PMA is absorbed through the human skin. No quantitative conclusions are possible. Studies on the absorption of PMA by the skin have not been carried out in laboratory animals. However, an aryl mercury compound, i.e., phenyl-mercury-dinaphtylmethane sulfonate, in aqueous solution was applied on the body surfaces of rabbits; mercury was found in the skin, subdermal connective tissue, and muscle (Ref. 44). The concentration of mercury in muscle was three times higher than that in the solution applied.

(d) *Metabolism and tissue uptake of PMA and inorganic mercury.* PMA is rapidly metabolized in the rat to yield inorganic Hg^{++} (Refs. 26 and 46). For instance, 48 hours after intramuscular injection of PMA into rats (Ref. 47), only 20 percent and 10 percent of the total mercury in the liver and kidney, respectively, was present as organic mercury. It seems appropriate, therefore,

to consider the distribution of mercury in the body following the administration of arylmercury, e.g., PMA and also of inorganic mercury, e.g., $HgCl_2$. Although the mercury compounds were administered by routes other than the intravaginal route, these studies are nonetheless pertinent since PMA is readily absorbed from the vagina, appearing in the blood and other tissues. The data obtained on intravenous injection of PMA and $HgCl_2$ are particularly relevant. The results obtained by the oral route of administration also need to be considered because some of the PMA applied intravaginally may be subsequently ingested.

Although there is no information available regarding the distribution of mercury in man following exposure to PMA or other arylmercury compounds, some generalizatons may be made from the animal studies. From data obtained mostly on mice and rats (Ref. 42), it may be noted that shortly after administration of PMA, the distribution pattern of mercury resembles that seen after administration of methylmercury, while later on it is closer to that seen after administering $HgCl_2$. This is due to metabolic cleavage of the covalent bond between the carbon and mercury atoms in the PMA molecule (Ref. 47) with a subsequent redistribution of Hg^{++}. The levels of mercury in the central nervous system after PMA administration are much lower than those seen after exposure to methylmercury but similar to those seen after exposure to $HgCl_2$. These results reflect the relative neurotoxicity of methylmercury, PMA, and $HgCl_2$—methylmercury being the most toxic of these compounds.

It may also be noted that the distribution changes with time regardless of whether PMA is given in a single administration or in repeated doses. In the rat (Ref. 28), a dynamic equilibrium is established 30 to 40 days after a single dose. It is also obvious (Ref. 42) that the levels of mercury found in the kidney are higher than levels in other organs. While high levels are also observed in the liver, the levels in the brain are relatively low.

Furthermore, blood has a high concentration of mercury immediately after administration of $HgCl_2$ by any route, but mercury is eliminated from blood faster than from most tissues in the body (Ref. 43). For the brain, the situation is the reverse—very little mercury penetrates into it, but once mercury has entered, the turnover is very slow. Suzuki, Miyama, and Katsunuma (Ref. 48) have shown that the elimination of mercury from the

mouse brain (i.e., half-life is 2 to 3 weeks) is slower than that from the other organs (i.e., half-life is about 1 week).

(e) *Distribution of mercury in the nervous system.* As discussed above, small amounts of mercury are taken up by the fetal and neonatal brain after exposure of the maternal organism to PMA or mercuric mercury. The distribution of mercury in various parts of the brain in early growth and development is not known. The following data on the mature brain have been obtained only recently.

Berlin and Ullberg (Refs. 27 and 28) made autoradiograms of whole-body sagittal sections of the pregnant mice after a single intravenous injection of PMA or mercuric chloride labeled with ^{203}Hg. The darkest areas, indicative of high radioconcentration, were found in the brain stem, the area postrema, hypothalamus, and in sites adjacent to the lateral ventricles. The gray substance of the cerebellum was darker than the surrounding tissue. The darkest areas of the brain indicated a radioconcentration comparable with that of the darkest areas of the liver on day 16 following the administration of $^{203}HgCl_2$; the results obtained with radioactive PMA were similar.

It appears that the brain takes up mercury slowly, but retains it for a long time in comparison with other organs; appreciable levels of mercury are attained only in parts which constitute a small fraction of the total brain tissue. Similar observations were made on the rat, rabbit, and squirrel monkey (Ref. 49), in experiments with radioactive elemental mercury (mercury vapor) and $Hg(NO_3)_2$. Autoradiography indicated similarities in the distribution of mercury in monkey brain regardless of the type of exposure; the highest radioconcentration was in the gray matter.

The guinea pig was studied in a like fashion by Nordberg and Serenius (Ref. 50); the results were similar. The authors advanced the important concept that the brain is a critical organ in mercury poisoning and that critical levels of mercury may be attained first in certain cells of the brain. The autoradiograms in these studies indicated that certain cells in the mesencephalon have a marked capacity for retaining mercury.

Chang and Hartmann (Refs. 51, 52, and 53) applied an electron-microscopic-histochemical method to study the general cellular as well as the precise intracellular localization and distribution of mercury in various parts of the nervous system after mercury intoxication. CH_3HgCl or $HgCl_2$ was

administered to rats orally or subcutaneously. The studies with $HgCl_2$ are particularly pertinent. In general, more mercury was detected in nervous tissues after methylmercury poisoning; and, regardless of the mercury compound used, increasing amounts of mercury were found in the nerve cells, neuroglia, and nerve fibers as the intoxications progressed. After the administration of $HgCl_2$, the general distribution of mercury in the nerve cells appeared to be in dorsal root ganglion neurons, Purkinje cells of the cerebellum, ventral horn motor neurons, calcarine cortical neurons, and granule cells of the cerebellum. As for the nerve fibers, regardless of the mercury compounds used, the general distribution of mercury was in dorsal root fibers, sciatic nerves, and ventral root fibers. Intracellularly, mercury was found binding to most of the membranous structures such as the mitochondria, the endoplasmic reticulum, the Golgi apparatus, and the nuclear envelope. In the nerve fibers, mercury was predominantly localized on the myelin sheaths and on the mitochondria. Biological membranes are generally rich in thiol or sulfhydryl $(-SH)$ groups, which may explain the preferential binding of mercury to the membranous structures.

Chang and Hartman (Ref. 53) also studied blood-brain barrier dysfunction in experimental mercury intoxication. Morphologically, the blood-brain barrier is described as a complex of very fine glial-limiting membranes surrounding the endothelium of the capillaries. Functionally, it acts not only as an obstacle to the passage of plasma solutes but also as a mediator of active biological transport securing the blood-brain exchange of metabolic material. It has been shown that in the regions of the hypothalamus, the neurohypophysis, and the area postrema there is a lack of glial membrane around some capillaries which suggests that the blood-brain barrier is weak and permeable in these regions. The authors applied a well-known technique, i.e., intracardial injection of a complex of toluidine blue and albumin, to ascertain the permeability of the brain. The mercury compounds administered to rats were methylmercury and $HgCl_2$; the latter compound is particularly pertinent. In each instance, "blue-brains" were obtained, suggesting a leakage of the protein-dye complex into the brain tissues. The brains of the dye-injected control animals were ivory-white; only a very slight bluish coloration was noted in some cerebral vasculatures and in the regions of the hypothalamus, the

hypophysis, and the area postrema. "Blue-brain" phenomena were not observed shortly after administration of the respective mercury compounds but only after 24 hours or even 1 week later. When frozen sections of these "blue-brains" were examined microscopically, blue dye could be detected in many nerve cells indicating that the injected dye had penetrated into the parenchyma of the brain. The results of this study on blood-brain barrier dysfunction in experimental mercury intoxication are consistent with the obervations of other investigators (Refs. 54 and 55) who observed a marked reduction in the uptake of amino acids by the nervous system after the administration of Hg^{++}.

It is noteworthy in this context that prolonged intoxication of rats with sublethal doses of methylmercury or $HgCl_2$ (Ref. 56) resulted in a decrease in the activity of certain enzymes (e.g., glucose-6-phosphatase, alkaline phosphatase, ATPase and succinic dehydrogenase) and an increase in acid phosphatase activity in the brain, kidney, and liver. The extent of the changes in enzyme activities appeared to be related to the amount of mercury distributed to each organ.

A study by Davis et al. (Ref. 57) on central nervous system intoxication from HgCl laxatives is relevant to the discussion of PMA because these mercury compounds share an important metabolic pathway. HgCl (calomel) furnishes Hg^+, which is converted in the body, in part at least, to Hg^{++}; PMA, as mentioned above, is metabolized to Hg^{++}. Calomel has been considered relatively nontoxic. The authors carried out quantitative, histochemical, and ultrastructural studies on the brain and certain other organs of two patients who developed dementia, erethism (excessive irritability to stimulation), colitis, and renal failure following the chronic ingestion of a laxative containing calomel. The levels from 21 areas of the brain ranged from 0.13 to 105.85 ug of mercury per g of tissue; the highest levels were in the inferior olive, red nucleus, and choroid plexus. Histochemical stains demonstrated mercury granules within the cytoplasm of neurons in these areas of the brain. It is clear from this study that in man, as in experimental animals, mercury accumulates preferentially in certain neuronal populations of the brain. This and related studies on calomel were recently reviewed by the Advisory Review Panel on OTC Laxative, Antidiarrheal, Emetic and Antiemetic Drug Products as published in the **Federal Register** of March 21, 1975 (40 FR 12913). In infants, administration of

calomel has caused a severe febrile (erythematous) disease known as acrodynia (pink disease) (Refs. 58, 59, and 60).

(f) *Distribution of mercury in the thyroid gland.* In view of earlier reports that exposure to mercury affects thyroid function, Suzuki, Miyama, and Katsunama (Ref. 61) investigated the retention of mercury in the thyroid gland. Rats or rabbits were injected subcutaneously with radioactive PMA, $Hg(NO_3)_2$ or methylmercuric acetate; the radioisotope was ^{203}Hg. PMA resembled mercuric nitrate in its distribution in the body. The mercury concentration in the thyroid was higher than that in the liver, brain, and blood but lower than that in the kidney (Ref. 61). It is noteworthy that the thyroid tends to retain mercury whereas the mercury levels in the liver and blood decline rapidly from day 7 to 14 following the injection. The concentration of mercury in the thyroid of the rabbit is lower than that in the kidney or liver. The follicle cells of the thyroid increase in height following exposure to mercury in all instances. The mercury is localized in the mitochondria of the follicle cells.

(g) *Effects of PMA and other mercury compounds on gonadal function and the gametes.* Berlin and Ullberg (Refs. 27 and 28) reported that mercury accumulates in several areas of the brain of pregnant mice, including an area corresponding to the hypothalamus. This observation prompted Lamperti and Printz (Ref. 62) to raise the questions of whether mercury interferes with the hypothalamic function, and whether that interference might be reflected in corresponding hormonal changes. To test whether mercury affects the reproductive cycle, female hamsters were injected subcutaneously with 1 mg of $HgCl_2$ per day on each day of the 4-day estrous cycle. Alterations were induced in the histology of the reproductive tract, progesterone levels, and cyclicity. The plasma progesterone levels were markedly reduced, and follicular development was retarded. It was suggested that mercury may have a direct effect on the ovary or hypothalamus.

Reproductive dysfunction in avian species exposed to $HgCl_2$ was observed by Thaxton and Parkhurst (Ref. 63). The authors allowed Japanese quail to drink, ad libitum, water containing $HgCl_2$ at the level of 125 u/mL. The reproductive efficiency (i.e., the number of mating attempts and eggs produced) was reduced drastically. The adverse effects of mercury on reproductive potential were not limited to the female; the male

was equally affected, e.g., the testis weight was reduced and there were fewer spermatogonia. It was suggested that mercury selectively inhibited the production of follicle-stimulating hormone (FSH) and/or luteinizing hormone (LH).

The possibility that mercury may be mutagenic as well as teratogenic is suggested by the following considerations. PMA and mercuric acetate, as noted above, induce embryopathic effects in the golden hamster (Ref. 34). Relatively high concentrations of mercury are found in the ovaries of mammals exposed to mercury compounds, e.g., mercaptomerin (a mercurial diuretic) concentrates in the follicular fluid (Ref. 64) and dimethylmercury in the walls of the larger follicles (Ref. 65). An increase in the number of exceptional daughter offspring (XXY) is induced in *Drosophila* with methyl- or phenyl-mercury (Ref. 66). To test the possibility that mercury may be mutagenic in mammals, Jagiello and Lin (Ref. 67) studied the potential of three mercury compounds to induce aberrations in the meiosis of mouse ova in vitro and in vivo. The compounds studied were mercaptomerin, dimethyl-mercury, and mercuric acetate; the latter compound is particularly pertinent since PMA is metabolized to furnish Hg $^{++}$. Although threshold levels of each compound were shown in vitro to induce severe effects on the nuclei of ova, i.e., retardation of meiotic progression or complete destruction of the chromosomes, no immediate or delayed effect could be demonstrated in vivo. The authors suggested that the mouse ovum is protected from the cellular effects of excess mercury by a barrier of unknown nature, perhaps residing in the zona pellucida, the vitelline membrane, or even the follicular cells. No extrapolation to potential effects of mercury on human ova in situ are possible since discrepancies have been shown to exist in the metabolic fate of various mercury compounds between species.

(2) *Effectiveness*—(i) *Sperm immobilization tests*. A vaginal suppository containing 0.4 mg PMA appeared to be less effective than other types of vaginal preparations (cream, foam, jelly) which did not contain mercury (Ref. 68 and 69). In tests employed by Johnson and Masters (Ref. 69), some of the nonmercurial preparations were shown to be highly effective in immobilizing sperm in vaginal specimens obtained from human subjects after artificial insemination.

(ii) *Clinical effectiveness*. The use-effectiveness of vaginal jellies containing PMA resulted in failure rates (pregnancies per 100 woman-years) ranging from 21 to 36 (Ref. 68); method failure was considerably lower, about 7.6. The failure rates obtained with nonmercurial vaginal preparations were similar, or in some studies much lower. Therefore, the Panel concludes that PMA is an effective contraceptive for OTC use.

(3) *Evaluation*. Although caution must be exercised in extrapolating to man the results of experimental studies on animals, it has been clearly established that PMA is absorbed from the human vagina, appearing in significant concentrations in blood and urine. In cases of contraceptive failure involving the use of vaginal preparations of PMA, overt symptoms of mercury poisoning have not been detected in infants, yet possible subclinical effects, e.g., delayed neurologic or intellectual damage, may have escaped detection. An epidemiological study to identify such subclinical effects does not seem feasible in view of the difficulties in recognizing a causal relation between birth defects and chemical agents. However, the special susceptibility of the fetus and child to chemical pollutants, such as mercury, and the seriousness of mercury poisoning are generally recognized.

Furthermore, the Panel notes that the effectiveness of certain nonmercurial vaginal contraceptive preparations is comparable to those containing PMA. Since a safe substitute for the mercurial preparation is available, the Panel's conclusions are in accordance with the general guidelines offered by the Secretary's Pesticide Advisory Committee, H.E.W. (1971) regarding the exercise of restraint in the use of any mercury compound and the search for safe substitutes (Ref. 70).

The Panel concludes from an extensive review of the submissions and the pertinent scientific literature that mercury compounds as active ingredients in some vaginal contraceptive preparations are potentially hazardous to the fetus and the breast-fed infant. Therefore, the Panel recommends that all vaginal contraceptives containing mercury compounds as active ingredients be placed in Category II since they are not generally recognized as safe.

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3. *Category II labeling.* The promotional material of other products unrelated to contraception which is included with contraceptive labeling can be misleading to the consumer. For example, certain contraceptive labeling includes promotional material for vaginal douche products. The Panel is aware that there is a long history of misunderstanding by the consumer as to the effectiveness of douching for contraception. It believes that the inclusion of such promotional material may be interpreted as an endorsement of douching as a contraceptive method or as an enhancement of the activity of the contraceptive product. Such labeling is considered misleading and is, therefore, placed in Category II.

The Panel considered at length the issues involved in labeling which makes comparisons among products, methods, and dosage forms, and labeling which expresses effectiveness as a numerical percentage (e.g., failure rate, percent of women for whom the product is effective under described use conditions, etc.). The Panel realizes that this type of labeling would be of greatest benefit to the consumer; however, it cannot recommend such labeling since there are no valid studies which would support comparative method-effectiveness or use-effectiveness claims. Furthermore, the studies that would be required to substantiate such claims are not feasible due to the size of claims are not feasible due to the size of the sample that would be needed, the variations in subject motivation for contraception, varying methods and habits of product use, and a number of other critical factors. Therefore, any comparative-effectiveness labeling is placed in Category II by this Panel. If, in the future, a manufacturer desires to label a product with such claims, the substantiating data must be submitted to the FDA through the new drug procedures.

The Panel further recommends that in order to make any numerical claims of effectiveness the manufacturer must disclose all effectiveness data used in developing such claims rather than disclosing the data selectively. (See part III. paragraph G. below—Testing Guidelines for Contraceptive Effectiveness.)

In reviewing the various claims submitted by manufacturers, the Panel found the following terms unacceptable for one or more of three reasons. Terms were placed in Category II when they were found (1) to exaggerate and promote impressions of unproven safety and/or effectiveness. (2) to be vague or poorly defined, or (3) to be unamenable to proof by scientific methods. While these three reasons may not be mutually exlusive, they do serve to define unacceptable labeling practices. Generally speaking, claims and phrases which include superlative terms which ascribe medical or authoritative approval, and terms which tend to exaggerate the safety, effectiveness, or public acceptance of a product are all considered misleading. The Panel classifies all such labeling as Category II for vaginal contraceptives.

a. *Claims that exaggerate and promote impressions of unproven effectiveness.*

"(10 hour) vaginal jelly."
"Medically approved."
"Medically tested."
"Medically supervised clinical studies."
"Most frequently prescribed by physicians."
"Special barrier base."
"Remarkable birth control invention."

b. *Claims that are vague or poorly defined.*

"Inexpensive."
"Ideal."
"Outstanding sperm effect in tests comparing it to other products."
"Instantly lethal to male sperm."
"Quality assurance."

c. *Claims that are unamenable to proof by scientific methods.*

"Unique."
"Exceptional ability."

D. *Category III Vaginal Contraceptive Ingredients*

1. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the reclassification of Category III conditions to Category I.

2. *Category III Active Ingredients.*

Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate)
Laureth 10S

Category III Combinations

Methoxypolyoxyethyleneglycol 550 laurate and nonoxynol 9

a. *Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate).* The Panel concludes that dodecaethylene glycol monolaurate is safe for OTC use but that data are insufficient to prove its effectiveness as a vaginal contraceptive.

(1) *Safety.* The Panel reviewed one study in which dodecaethylene glycol monolaurate was instilled intravaginally into 21 rabbits once daily for 21 consecutive days without any adverse effect (Ref. 1). A second study reported that application of the ingredient to the conjunctiva of 30 rabbits resulted in no local irritation or adverse effect (Ref. 1).

In evaluating human safety, the Panel is aware of one study of dodecaethylene glycol monolaurate. A jelly preparation containing this ingredient at a concentration of 5 percent (the strength of the currently marketed product) was instilled intravaginally into 50 females once nightly for periods of 10 to 21 nights. Vaginal examinations and smears done by the investigator, and personal observations by the subjects, demonstrated no irritations, side effects, or other problems (Ref. 1). Therefore, the Panel concludes that dedecaethylene glycol monolaurate is safe for OTC use.

(2) *Effectiveness.* Dedecaethylene glycol monolaurate was studied from the standpoint of how well it interferes with the passage of sperm (Ref. 1). In this barrier action study, using only one human subject, there was photographic evidence of cervical occlusion for up to 10 hours after application of the drug. There were no data submitted on the effectiveness of this ingredient alone (in vitro), and there were no data presented on postcoital human testing or animal antifertility testing of the formulation. Although clinical effectiveness data on formulations containing this ingredient were submitted, the Panel concludes that these data are insufficient at this time to determine the effectiveness of dodecaethylene glycol monolaurate as a contraceptive for OTC use.

(3) *Dosage.* A single dose of the product must deliver the active ingredient in concentrations which as a minimum meet those standards of acceptability set forth in the effectiveness-testing section of this document. (See part III. paragraph G.1. below—Tesing Guidelines for Contraceptive Effectiveness).

(4) *Labeling.* The Panel recommends the Category I labeling for contraceptive ingredients. (See part III. paragraph B.3.

above—Category I labeling for vaginal contraceptive drug products.)

(5) *Directions.* The amount of the formulation to be used and the optimum time prior to intercourse at which the spermicide should be used varies with the formulation. Specific directions for use will be determined from the data derived from the required testing for each product. The directions must clearly indicate the amount of the product to be instilled in the vagina and how long prior to intercourse this must be done in order to produce effective contraception. Additionally, the period of time during which the product can be expected to retain its effectiveness must be stated. Other nonspecific labeling is outlined earlier in this document. (See part II. paragraph G.5. above—Directions for use and part III. paragraph B.3. above—Category I labeling for vaginal contraceptive drug products.)

(6) *Evaluation.* The Panel recommends that dodecaethylene glycol monolaurate be subjected to the testing procedures outlined below, in order to prove contraceptive effectiveness. (See part III, paragraph G. below—Testing Guidelines for Contraceptive Effectiveness.)

References

(1) OTC Volume 110020.

b. *Laureth 10S.* The Panel concludes that laureth 10S, a nonionic surfactant, is safe for OTC use but that data are insufficient to prove its effectiveness as a vaginal contraceptive.

(1) *Safety.* The Panel reviewed several animal studies utilizing this ingredient. In one test which was conducted to determine whether or not laureth 10S, at 2- and 5-percent concentrations, produced irritation or toxicity when inserted daily into the vaginas of dogs for a 3-month period, the following results were recorded: First, the animals receiving both concentrations experienced much discomfort when the jelly was inserted; second, vaginal and vulvar inflammation resulted during the use of the laureth 10S at both concentrations, but when the ingredient was withheld for 2-day periods, the inflammation subsided; third, after the experiment, a histological examination of the liver, kidney, spleen, and vagina showed no evidence of any damage due to the laureth 10S (Ref. 1). In another test, when the ingredient was administered in a 5-percent concentration to a group of test dogs, using both a jelly base and a formulation containing saline, the saline formula produced a definite erythema (abnormal redness) of the vaginal wall;

but the jelly base preparation produced no vulvar or vaginal irritation (Ref. 1).

A long-term intravaginal toxicity study was performed in dogs using two foam preparations containing the active ingredient. The more concentrated foam contained 10-percent active ingredient. The concentration of the other foam and the inactive ingredients were not given in the submission. At the conclusion of the experiment, no histologic changes were found in the kidneys, spleens, livers, and vaginas of animals in either test group. Likewise, urinary and hematologic studies did not show any significant changes (Ref. 1).

A single reproductive study which was conducted using rabbits was submitted to the Panel. Mated females were given 1 g of the foam preparation intravaginally 5 days a week from the fifth day of pregnancy to term. This did not result in any reduction in the size of the litters or any abnormalities in the offspring (Ref. 1).

The Panel reviewed one study of the safety of laureth 10S in humans. A jely formulation of the drug in a 2-percent concentration was administered intravaginally (daily for 21 days) to a group of 10 subjects with no adverse effects (Ref. 1). The Panel concludes that laureth 10S is safe for OTC use.

(2) *Effectiveness.* There were no data presented on in vitro studies of the ingredient alone or in formulation. In addition, there was no evidence of postcoital testing or animal antifertility studies of the formulation presented to the Panel. Therefore, the Panel concludes that data are insufficient at this time to determine the effectiveness of laureth 10S as a contraceptive for OTC use.

(3) *Proposed dosage.* A single dose of the product must deliver the active ingredient in concentrations which as a minimum meet those standards of acceptability set forth in the effectiveness-testing section of this document. (See part III. paragraph G.1. below—Testing Guidelines for Contraceptive Effectiveness.)

(4) *Labeling.* The Panel recommends the Category I labeling for contraceptive ingredients. (See part III. paragraph B.3. above—Category I labeling for vaginal contraceptive drug products.)

(5) *Directions.* The amount of the formulation to be used and the optimum time prior to intercourse at which the spermicide should be used varies with the formulation. Specific directions for use will be determined from the data derived from the required testing for each product. The directions must clearly indicate the amount of the product to be placed in the vagina and how long prior to intercourse this must

be done in order to produce effective contraception. Additionally, the period of time during which the product can be expected to retain its effectiveness must be stated. Other nonspecific labeling is outlined earlier in this document. (See part II. paragraph G.5. above—Directions for use and Part III. paragraph B.3. above—Category I labeling for vaginal contraceptive drug products.)

(6) *Evaluation.* The Panel recommends that laureth 10S be subjected to the testing procedures outlined below in order to prove contraceptive effectiveness. (See part III. paragraph G. below—Testing Guidelines for Contraceptive Effectiveness.)

References

(1) OTC Volume 110021.

c. *Methoxypolyoxyethyleneglycol 550 laurate and nonoxynol 9.* The Panel concludes that the combination of methoxypolyoxyethyleneglycol 550 laurate and nonoxynol 9 is safe for OTC use but that data are insufficient to prove its effectiveness as a vaginal contraceptive.

(1) *Safety.* Tests in which rabbits and mice received vaginal applications of methoxypolyoxyethyleneglycol 550 laurate for 21 days resulted in no irritations. Similarly, no irritation was produced when this ingredient was applied to the conjunctiva of rabbits (Ref. 1). In the reports on clinical testing, the Panel noted that there was no local (vaginal) irritation observed in the test subjects. The Panel, therefore, concludes that this ingredient is safe for OTC use. From the safety testing performed on nonoxynol 9, the Panel concluded that it was safe for OTC use. (See part III. paragraph B.2.b. above—Nonoxynol 9.) The Panel also concludes that the combination of methoxypolyoxytheleneglycol 550 laurate and nonoxynol 9 is safe for OTC use.

(2) *Effectiveness.* Methoxypolyoxyethyleneglycol 550 laurate is marketed in combination with nonoxynol 9 (another nonionic surfactant), and the data submitted were only on the combination product. Although the Panel concluded that nonoxynol 9 is effective (see part III. paragraph B.2.b. above—Nonoxynol 9), no in vitro, postcoital, or animal antifertility data were presented on methoxypolyoxyethyleneglycol 550 laurate alone. Additionally, there are no clinical studies which have been done on this ingredient as the sole contraceptive agent in a formulated product. Therefore, the Panel concludes that the data are insufficient at this time to determine the effectiveness of the

combination of methoxypolyoxyethyleneglycol 550 laurate and nonoxynol 9 as a contraceptive for OTC use.

(3) *Proposed dosage.* A single dose of the product must deliver the active ingredient in concentrations which as a minimum meet those standards of acceptability set forth in the effectiveness-testing section of this document. (See part III. paragraph G.1. below—Testing Guidelines for Contraceptive Effectiveness.)

(4) *Labeling.* The Panel recommends the Category I labeling for contraceptive ingredients. (See part III. paragraph B.3. above—Category I labeling for vaginal contraceptive drug products.)

(5) *Directions.* The amount of the formulation to be used and the optimum time prior to intercourse at which the spermicide should be used varies with the formulation. Specific directions for use will be determined from the data derived from the required testing for each product. The directions must clearly indicate the amount of the product to be instilled in the vagina and how long prior to intercourse this must be done in order to produce effective contraception. Additionally, the period of time during which the product can be expected to retain its effectiveness must be stated. Other nonspecific labeling is outlined earlier in this document. (See part II. paragraph G.5. above—Directions for use and part III. paragraph B.3. above—Category I labeling for vaginal contraceptive drug products.)

(6) *Evaluation.* The Panel recommends that methoxypolyoxyethyleneglycol 550 laurate be subjected to the testing procedures outlined below in order to prove contraceptive effectiveness. (See part III. paragraph G. below—Testing Guidelines for Contraceptive Effectiveness.)

References

(1) OTC Volume 110016.

E. *Inactive Ingredients—Comment on Safety.* Although this review is primarily an evaluation of the safety, effectiveness, and labeling of active ingredients in OTC vaginal drug products, the Panel has determined that some of the inactive ingredients present in vaginal contraceptive products are of questionable safety. Those groups of drugs which concerned the Panel were first, the quaternary ammonium compounds (benzethonium chloride and methylbenzethonium chloride) which are used as preservatives, and second, boron-containing compounds (boric acid, sodium borate, sodium perborate) which have not been shown to be safe in

concentrations yielding greater than 1.0-percent boron.

1. *Quaternary ammonium compounds (benzethonium chloride and methylbenzethonium chloride).* In its evaluation of the submitted data, the Panel has noted that the quaternary ammonium compounds were first received enthusiastically as detergent disinfectants. However, after careful review of these ingredients, it has concluded that there is significant doubt about the claimed antibacterial action and safety of these compounds. Bacterial contamination of aqueous benzalkonium chloride and of swabs sterilized with aqueous benzethonium chloride has been reported. Outbreaks of *Pseudomonas* bacteremia in several hospitals have been shown to be due to the use of contaminated solutions of quaternary ammonium compounds (Refs. 1 through 5). Warnings and comments on the use of quaternaries for wet sterilization have recently appeared in editorials in several of the leading medical journals (Refs. 6, 7, and 8).

The question of effectiveness and the potential dangers associated with the use of these compounds are based on several observations. The quaternaries are inactivated by soaps, anionic compounds, and anionic surfactants. They are selectively adsorbed on a variety of surfaces, including proteinaceous surfaces, gauze, cellulose, cork, and plastics. When applied to skin, they may form a film which is sterile on the outer surface (the hydrophilic part of the molecule), but contaminated on the under surface (the lipophilic part of the molecule), which orients towards the skin. Furthermore, since they are used in bacterial culture media to prevent the overgrowth of other organisms so that *Pseudomonas* can grow, they may actually promote the growth of *Pseudomonas* organisms. Thus, in addition to a large body of evidence demonstrating the relative ineffectiveness of quaternary compounds as bactericidal agents, there are significant concerns about their safety.

During the long marketing history of suppositories and other contraceptive products containing quaternaries, there have been no reports of clusters of vaginal or pelvic infection. Nevertheless, without specific investigation of these conditions the role that quaternaries may play in vaginal contamination by potentially pathogenic organisms will remain unknown.

The Panel, therefore, concludes that the safety and effectiveness of the quaternary ammonium compounds as preservatives in vaginal compounds are still in question.

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2. *Boron compounds (boric acid and sodium borate).* In several of the contraceptive preparations reviewed by this Panel, boric acid and sodium borate are present in small doses as preservatives or as pharmaceutical necessities, without any claims for their spermicidal action. At low concentrations (less than 1 percent) boric acid and its sodium salt are considered to be safe and effective as preservatives in vaginal products. However, these concentration, must not be exceeded because a question of safety exists with the use of boron compounds at greater than preservative levels. The Panel believes that FDA should closely monitor all vaginal drug products which contain boron compounds to ensure that the consentrations do not exceed that which is necessary for preserving the product from bacterial contamination. (Further discussions and recommendations regarding boric acid, boroglycerine, sodium borate, and sodium perborate will be published in the Panel's review of other vaginal drug products which will appear in a future issue of the Federal Register.)

F. Testing Guidelines for Contraceptive Safety

Safety testing guidelines for all vaginally applied ingredients are discussed elsewhere in this document. (See part II. paragraph D. above—Drug Evaluation for Safety.)

G. Testing Guidelines for Contraceptive Effectiveness

At the present time, no specific guidelines have been provided by the FDA for testing the contraceptive effectiveness of vaginal products or for testing the validity of numerically expressed claims of effectiveness. The Panel, therefore, recommends that the following guidelines be used both for the evaluation of products intended for use as vaginal contraceptive agents and for the substantiation of numerically expressed or comparative claims.

From long-term marketing experience, certain vaginal contraceptives containing Category I ingredients have been shown to be effective. Certain of these products will require in vitro spermicidal testing to establish the dose range; no animal testing will be required. However, clinical testing under the more carefully controlled conditions described below will be required for any formulation containing ingredients assigned to Category III. Furthermore, the Panel concludes that the following set of guidelines should serve as minimal standards for the testing and evaluation of any new vaginal contraceptive drug and products.

To establish the contraceptive effectiveness of a vaginal product, in vitro testing, animal testing, and clinical testing should be carried out in the following sequence.

1. *In vitro testing.* In vitro studies, as emphasized by McConnel (Ref. 1), should be designed to test the mode of action of the contraceptive formulation in question. While most vaginal contraceptive formulations appear to be either spermicidal or sperm immobilizing, other compounds may have different modes of action. For instance, compounds such as 1-chloro-3-tosylamido-7-amino-2-heptanone hydrochloride (TLCK) interfere with fertilization by inhibiting certain enzyme activity necessary for the sperm to penetrate the ova (Ref. 2). Regarding related modes of the action of contraceptive agents, Davajan et al. (Ref. 3) have reviewed in vitro tests which allow quantitative assessment of spermicidal action by measuring the passage of sperm through human cervical mucus obtained at midcycle. During a presentation to the Panel, Blandau suggested, on the basis of his experimental studies, that bovine cervical mucus may be substituted for human cervical mucus when determining the resistance of cervical mucus to sperm penetration. This procedure would simulate the in vivo situation in which sperm and cervical mucus interact and would take into consideration additional mode of action of the vaginal contraceptive formulation, i.e., the enhancement of the resistance of the cervical mucus to the passage of sperm (Ref. 4).

The in vitro screening tests for spermicidal or sperm-immobilizing activity listed below have been reviewed by the Panel. In order for a compound to be considered an effective contraceptive formulation, it must meet one of two requirements. First, it must act rapidly and efficiently, killing or immobilizing all sperm on contact; or second, it must render the sperm incapable of fertilization. When the spermicidal formulation is delivered initially in a solid vehicle, the active ingredient must become available 10 to 15 minutes after insertion.

Several systems for in vitro testing using human semen have been devised and used in various laboratories. Five have been in general use: the Brown and Gamble (Ref. 5); the Sander and Cramer (Ref. 6); those developed by Baker, Ronson, and Tynen (Ref. 7); the saturation or titration test devised by Mende and Berliner (referenced in the Millman study, Ref. 8); and the International Planned Parenthood Federation Agreed Test for Total Spermicidal Power (IPPF Agreed Test) (Ref. 9) based on work by Harris (Ref. 10). The IPPF Agreed Test is currently being used by most laboratories as the standard spermicide screening procedure.

Vehicles for spermicides may serve multiple functions and require evaluation as well. For instance, the vehicle may act not only as a carrier for the spermicide by may serve also as a physical barrier, either prohibiting sperm access to the cervical canal or slowing sperm motility (Ref. 1). However, the Panel recognizes that the vehicle may also negatively influence the activity of the contained ingredients. It is concerned, for instance, about the contraceptive effectiveness of an ingredient delivered in a vaginal suppository or tablet, since factors such as proper placement, time required for melting, and duration of action have not always been sufficiently well-documented. The Panel concludes that the spermicidal effectiveness of the final formulation must be demonstrated by in vitro testing.

To that end, the Panel considered the available methods of in vitro testing mentioned above. Of these, the IPPF Agreed Test appears to be the most widely used. In 1969, 87 percent of the spermicidal contraceptives available in the United Kingdom and 66 percent of those available in the United States had been tested by this method (Ref. 11). In addition, the detailed lboratory methods involved in performing the IPPF Agreed Test have been published widely, whereas the methodology of the other in vitro testing procedures is less rigorous. Therefore, the Panel recommends that the following in vitro testing procedure, derived from the IPPF Agreed Test, be required as the minimum standard for demonstrating the spermicidal effectiveness of vaginal contraceptive drug products.

a. *General criteria for effectiveness testing.* To qualify as effective, the final formulation of a vaginal contraceptive product must meet or exceed the criteria established in this protocol. Accordingly, the product reaches a desirable level of spermicidal activity provided 1.0 milliliter (mL) of a 1:11 solution of the product in sline kills all sperms in 0.2 mL of semen under the conditions of the test as described below. Each product should be tested against semen from three different individuals; if all sperm are killed in these three samples, then the product is accepted. If it fails to do this in two out of three or in all three, then it is regarded as unacceptable. If it fails with one semen sample, then the whole test is repeated using three different semen samples; and only if it kills all sperm in all of these new semen samples can it be regarded as having reached a desirable level of spermicidal activity. In other words, only one fail is permitted out of six tests.

b. *Apparatus and reagents.*
(1) 0.9 percent weight to volume (w/v) saline solution.
(2) Buffered glucose solution: Dissolve 3.0 grams (g) glucose, 0.24 g anhydrous disodium phosphate (0.45 g disodium phosphate heptahydrate), 0.01 g potassium phosphate, and 0.2 g sodium chloride in distilled water to make 100 mL.
(3) Magnetic stirrer.
(4) Stainless steel lockwasher (1.2X0.2 centimeters (cm)) or other suitable magnetic stirring bar.
(5) Glass or polyethylene-coated magnetic stirring bar.
(6) Test tubes, 85X15 mL, thick walled.
(7) Beakers, 50 mL.
(8) Pipettes as required.
(9) Timer.
(10) Microscope.

(11) Incubator or water bath (at 35 to 37° C).

(12) pH meter, equipped with glass and saturated calomel electrodes.

c. *Minimal requirements for semen to be used for testing.*

(1) *Sample collection and storage:* Specimens must not be collected in a rubber or latex sheath or condom and should be kept tightly stoppered in a tube at room temperature before being tested.

(2) *Sample age:* Not more than 4 hours. old.

(3) *Density:* Not less than 50 million per milliliter.

(4) *Motility:* 40 to 50 percent of the sperm should show rapid forward motion when examined with a fresh mount at 35 to 37° C.

(5) *Viscosity:* Properly liquefied semen, not "stringy" when run out of a pipette, and appearing homogeneous to the naked eye.

d. *Control test for the effect of dilution and mixing on sperm activity.* The following control test should be done on each specimen of semen just before it is used for the spermicidal tests. If the semen is in use for more than 2 hours, the control test should be repeated.

(1) Bring all materials to 35 to 37° C, using incubator or waterbath.

(2) Pipette 0.2 mL of semen into test tube, taking care that no semen splashes up the sides of the tube.

(3) Add lockwasher or other magnetic stirring bar, insert tube in field of magnetic stirrer.

(4) Add 1.0 mL of saline, simultaneously starting stirrer and timer. This is zero time.

(5) Let mix for 10 seconds. Place a drop on a plain slide, cover with cover-slip, and put on microscope stage.

(6) At 40 seconds (i.e., 30 seconds after end of mixing) rapidly examine 5 fields with low power (100 to 150 X), followed by 5 fields with high power (400 to 600 X).

(7) If activity in the dilution is not satisfactory in terms of the original assessment, the sample of semen must be discarded.

(8) Add 1.0 mL of buffered glucose solution, mix, and reexamine for sperm activity after 30 minutes at 37° C.

e. *Testing for spermicidal effectiveness.* Dilutions of spermicidal products should be made up freshly with a 0.9-percent saline solution, just before the test is to be done. 1.0 g of the product is weighed into a 50-mL beaker and 11.0 mL of normal saline are added; this solution is kept at 35 to 37° C for 15 minutes. After this period, the spermicidal solution is stirred for 15 minutes at 35 to 37 C if possible, otherwise at room temperature (22 to 25°

C), using a glass or polyethylene-coated magnetic stirrer. Following this stirring the solution is allowed to stand at 35 to 37° C for 30 minutes. Immediately before each test the spermicidal solution is stirred 20 times, using a glass rod. The pH of the solution is recorded with a pH meter. In the case of foaming tablets, one reading is taken while foaming is in progress, and a second reading is taken when foam is completely exhausted.

(1) Bring all material to 35 to 37° C, using incubator or waterbath.

(2) Place 0.2 mL of warm semen in test tube, taking care that no semen splashes up the sides of the test tube, since this might cause a false fail.

(3) Add lockwasher or other magnetic stirring bar; insert tube in field of magnetic stirrer.

(4) Add 1.0 mL of the warm spermicidal solution prepared as above, simultaneously starting stirrer and timer. This is zero time.

(5) Let stir for 10 seconds. Place a drop on a plain slide, cover with cover-slip, and put on microscope stage.

(6) At 40 seconds examine 5 fields rapidly with low power (100 to 150 X). If no motility is observed, confirm by examining at least 5 fields under high power (400 to 600 X). If even a single sperm shows any sign of life, i.e., jerking or swimming, score "fail." If no sperms show any sign of life, score "preliminary pass."

(7) If no active sperm are found, add 1.0 mL of buffered glucose solution to the tube containing the semen-spermicide mixture. Stir well with glass rod or mix well by drawing the fluid into pipette and running out three times. Place in incubator for about 30 minutes and reexamine as above. If still no active sperm are seen, score "final pass."

f. *Test data retention.* All raw data generated as a result of this testing for every product formulation shall be retained and shall be indexed by product identification and the date of the study. The manufacturer shall permit an authorized employee to the FDA at a reasonable time and in a reasonable manner to inspect and copy all such records. If the manufacturer refuses to permit such inspection or fails to retain such test data, the FDA will take action to prohibit further marketing of the product.

g. *Test modifications.* The formulation of certain products may require modification of this in vitro testing procedure. Any proposed modification shall be submitted with supporting documentation (preferably in quadruplicate) to the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–62, 5600 Fishers

Lane, Rockville, MD 20857. The Director, Division of OTC Drug Evaluation, shall notify the applicant in writing of the agency's decision regarding the requested test modification. All such requests and the agency's response shall be maintained in a permanent file for public review at the office of the Hearing Clerk.

2. *In vivo testing*—a. *Animal testing.* The Panel recommends that testing for contraceptive effectiveness be required in two appropriate animal species, although it is aware that insufficient work has been done toward the development of animal models for this purpose. The relevance of a particular animal model system will depend on the postulated mode of contraceptive action of the vaginal preparation. For instance, if interference with sperm transport is postulated, the following observations must be considered. In humans, in most nonhuman primates, and in ruminants (e.g., sheep, oxen, etc.), semen is deposited in the vagina; whereas, in the horse, pig, dog, and in murine rodents, semen is deposited directly into the uterine lumen (Ref. 12). The latter species would, therefore, appear to be inappropriate as animal test models.

Although Hartman (referenced in the Millman study, Ref. 8) and Chang (Ref. 13) have both used the rabbit as a test model for vaginal antifertility agents, they have shown that most human spermicides were relatively ineffective in the rabbit when pregnancy rates were used as an index. However, the rabbit may be an adequate model to assess vaginal contraceptive agents (even though pregnancy is not completely inhibited) because recent studies have indicated that implantation rates can be used as a measure of vaginal contraceptive potency (Ref. 14).

It should be pointed out that tests for the effectiveness of vaginal contraceptives should be performed during the fertilizable lifetime of the ovum. And the more closely that such studies simulate the human situation, the more significant they would be. In this regard, the usefulness of the stump-tailed macaque (*Macacca arctoides*) has been reported recently by Bhattacharyya and Zaneveld (Ref. 15) and by Zaneveld et al. (Ref. 16). The Panel encourages the further development of this promising primate model for testing vaginal contraceptive effectiveness. The use of nonhuman primates in research on human reproduction has been extensively reviewed by Diczfalusy and Standley (Ref. 17).

The use of farm animals, particularly sheep, also merits consideration since the reporductive performance of

domestic animals and their fertility is well-understood. These animals have been used to study the effects of other methods of fertility control (Ref. 18) and may prove useful in the evaluation of vaginal contraceptive agents.

b. *Human effectiveness testing.* Testing for contraceptive effectiveness of vaginal products in humans has been poorly standardized. Likewise, the evaluation of those products on the market has shown wide ranges of effectiveness of the same product in different studies. The difficulty arises in the wider variance in use-effectiveness than in method-effectiveness. Studies are limited by the inappropriateness of using controls (placebo) and by the variation in the methods of statistical analysis of data. Although most results have been computed by the Pearl Formula (Ref. 19) and a few by the Life-Table method (Ref. 20), the two methods are in no way comparable. The Pearl Formula expresses method-failure rates in pregnancies per woman per year; the Life-Table method corrects for the variability in fertility rates as well as other variables.

For example, a large retrospective study in 1970 revealed that the use-effectiveness for foam products was 69 percent by the Pearl method (Ref. 21). This study was limited by the fact that it depended on patient recall. Other large prospective studies have shown failure rates as low as 3.14 percent and 3.98 percent (Refs. 22 and 23). The validity of the first of these studies was limited by a large dropout rate and by short-term usage of the product. The second was a better study in that it involved 2,932 patients of whom a significant number continued for more than 12 months.

Similar wide variations in effectiveness are reported in studies with jellies, creams, and suppositories (Ref. 24). Because of the wide range in results, the Panel found it very difficult to establish an acceptable standard of effectiveness which should be required for future products. It has, therefore, devised the following protocol for long-term prospective studies in order to establish a more accurate effectiveness standard for there products.

The effectivenes of vaginal contraceptive drug products which are to be used exclusively in conjunction with a diaphragm can only be determined by clinical studies. The Panel, therefore, recommends that such products be subjected to Phase I, Phase II, and Phase III of the clinical effectiveness testing program outlined below.

The sample size, i.e., the number of subjects, for each phase of study is given below merely for purposes of

illustration. The actual sample size required is dependent upon two major factors: (1) The objective of the study and (2) the level of statistical significance required to support the conclusions drawn from the study. Methods for statistical evaluation of data on contraceptive effectiveness have been devised (Ref. 19). The Panel concludes that these methods are acceptable.

The Panel recommends that appropriate informed consent should be obtained from all study participants in accordance with § 310.102 (21 CFR 310.102). Guidelines for how such informed consent is to be obtained are available from the Division of Research Grants, the National Institutes of Health, Bethesda, MD 20014. The Panel is aware the FDA will publish a proposed regulation in a future issue of the Federal Register which will set forth procedures for obtaining informed consent.

Note.—The FDA proposed regulation on informed consent was published in the Federal Register of August 14, 1979 (44 FR 47713)).

(1) *Phase 1.* Short-term tolerance studies should be performed before embarking on any long-term programs. A study of the effect of increasing dosages, based on initial evaluation in animals, should be performed in 10 to 20 subjects using the product for at least 10 days. These subjects should be carefully evaluated for any evidence of local or generalized reaction before proceeding to Phase II. Also included in the Phase I testing would be an appropriate postcoital test such as those described by Huhner (referenced in the Davajan and Kunitake article, Ref. 25) or Johnson and Masters (Ref. 26).

(2) *Phase II.* At least 50 subjects should use the product in the recommended dosage and in accordance with the recommended method of application for 6 months to determine short-term effectiveness before proceeding to the long-term studies. The following minimal criteria should be used for selection of test subjects:

(i) Age 18 to 35 years.

(ii) Normal past medical history and normal physical examination.

(iii) No known pelvic pathology or infertility unless followed by an uneventful intrauterine pregnancy.

(iv) Previous proven fertility of the same couple (Phase II only).

(v) Menstruating regularly (at least 2 periods in the previous 3 months).

(vi) Regular coitus by history (at least two times per week).

(vii) The subject should use no other contraceptive method.

The following conditions of use should prevail:

(i) The product should be used in the anticipated recommended dose.

(ii) The product should be administered according to anticipated labeling instructions.

(iii) Prior to enrolling in the study, the subject must demonstrate to the investigator her ability to administer the product into the vagina.

(iv) The times of application and times of coitus and menstrual history must be carefully recorded (Phase II only).

Those subjects who continue into Phase III should be followed in accordance with the study protocol, and those who do not continue into Phase III should be followed through one additional normal menstrual period.

(3) *Phase III (method-effectiveness).* This Panel has previously defined method-effectiveness as that rate of effectiveness obtained in a well-controlled clinical study using highly motivated subjects. If acceptable pregnancy protection rates are demonstrated in Phase II testing, the same protocol will be used for long-term studies with the exceptions noted above. A sufficient number of volunteers should be enrolled so that a minimum of 200 will complete 12 months in the study. Significant fertility reduction must be demonstrated as required in the Phase II testing guidelines above. All data are to be analyzed by use of the Life-Table method.

(4) *Phase IV (use-effectiveness).* This Panel has previously defined use-effectiveness as that rate of effectiveness obtained when the product is used by a large number of subjects under real-life conditions (widespread general usage). It is imperative to note that the Panel does not recommend that use-effectiveness data be required in order to prove the effectiveness of a vaginal contraceptive product; only Phases I, II, and III are required. Phase IV guidelines are offered only for the substantiation of numerically expressed claims of effectiveness.

Use-effectiveness should be determined for different categories of users. For instance, a very important category would include those women most likely to be successful contraceptors: Women whose last pregnancy was planned, i.e., preceded by contraception which was discontinued in order to achieve pregnancy, and who have achieved their desired family size. Another important category would be based on the relative age of the user. Relative age is a combination of the woman's age and the number of children that she has had at the beginning of a specific birth interval

(Ref. 21). It has been shown that the failure rate or the rate of accidental pregnancy varies significantly according to the relative age of the user at the time of contraceptive failure.

Since the use-effectiveness of a vaginal contraceptive may change over a period of time as the characteristics of the population of women using the method change, the studies must be repeated at reasonable intervals. Also for this reason, studies which were carried out years ago may need to be repeated.

An effort should be made to obtain data not only on users within the health care system, e.g., in family planning clinics, but also outside this system since most users of OTC vaginal contraceptives fall into the latter group. Effectiveness data may be difficult to obtain although marketing survey methods have been used successfully in the past to obtain information on the awareness, usage, and attitude of the users toward the vaginal products.

c. *Extended use-effectiveness.* This Panel has previously defined use-effectiveness as that rate of effectiveness obtained when the product is used by a large number of subjects under real-life conditions (widespread general usage) over an extended period of time. As with Phase IV (use-effectiveness) testing, the Panel does not recommend that extended use-effectiveness data be required in order to prove the effectiveness of a vaginal contraceptive product; only Phase I, II, and III, are required. Extended use-effectiveness guidelines are offered only for the further substantiation of numerically-expressed claims of effectiveness.

A household survey methodology is best suited for evaluating the extended use-effectiveness of vaginal contraceptives. The survey should include but not be limited to information on age, race, number of children, contraceptive intent (e.g., spacing or prevention of pregnancy), marital status, coital frequency or exposure to risk, duration of use, history of pregnancies, contraceptive history within the study interval, educational level, employment, and use status at the end of the study (e.g., active user became pregnant under what circumstances, or use was discontinued for what reasons?). Documentation of these variables must be made.

d. *Data analysis.* The data from all effectiveness studies should be evaluated by the Life-Table method (Ref. 20). The Life-Table has replaced the traditional Pearl formula because it makes possible valid comparisons among studies extending over different

periods. Although previous data analyzed according to the Pearl formula may be salvaged by recalculation using the Life-Table method, new data will be required for a more precise evaluation. The data may be expressed as the percentage of women who become pregnant while using the method during the course of 1 year, i.e., the rate of accidental pregnancy.

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The agency has determined that under 21 CFR 25.24(d)(9) (proposed in the **Federal Register** of December 11, 1979; 44 FR 71742) this proposal is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under authority delegated to the Commissioner (21 CFR 5.1), it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal

Regulations be amended by adding new Part 351, to read as follows:

PART 351—VAGINAL CONTRACEPTIVE AND OTHER VAGINAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—Vaginal Contraceptive Drug Products; General Provisions

Sec.
351.1   Scope.
351.3   Definition.

Active Ingredients

351.10   Vaginal contraceptive active ingredients.
351.20   Permitted combinations of active ingredients. [Reserved]

Testing Procedures

351.30   In Vitro testing for spermicidal effectiveness.

Labeling

351.50   Labeling of vaginal contraceptive drug products.
351.52   Principal display panel.
351.54   Label.
351.56   Labeling.

Authority: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055-1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371; (5 US.C. 553, 554, 702, 703, 704).

SUBPART A—VAGINAL CONTRACEPTIVE DRUG PRODUCTS; GENERAL PROVISIONS

§ 351.1   Scope.

An over-the-counter vaginal contraceptive drug product in a form suitable for vaginal administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this Part 351 in addition to each of the general conditions established in § 330.1 of this chapter.

351.3   Definition.

A Vaginal contraceptive drug is a drug product which is placed in the vagina prior to intercourse for the purpose of preventing pregnancy.

Active Ingredients

§ 351.10   Vaginal contraceptive active ingredients,

The active ingredients of the product consist of any one of the following substances which is present in the product at a concentration which, meets those standards of acceptability set forth in § 351.30.

(a) Menfegol.
(c) Nonoxynol 9.
(c) Octoxynol 9.

§ 351.20   Permitted combinations of active ingredients. [Reserved]

Testing Procedures

§ 351.30   In vitro testing for spermicidal effectiveness.

(a) *General criteria.* To qualify as effective, the final formulation of a vaginal contraceptive product must meet or exceed the criteria established in this subpart. According to this protocol, the product reaches a desirable level of spermicidal activity provided 1.0 milliliter of a 1:11 solution of the product in saline kills all sperm in 0.2 milliliter of semen under the conditions of the test as described below. Each product should be tested against semen from three different individuals; if all sperm are killed in these three samples, then the product is accepted. If it fails to do this in two out of three or in all three semen samples, then it is regarded as unacceptable. If it fails with one semen sample, then the whole test is repeated using three different semen samples, and only if it kills all sperm in all of these new semen samples can it be regarded as having reached a desirable level of spermicidal activity;—in other words, only one fail is permitted out of six tests.

(b) *Apparatus and reagents.* (1) 0.9 percent weight to volume (w/v) saline solution.
(2) Buffered glucose solution: Dissolve 3.0 grams glucose, 0.24 gram anhydrous disodium phosphate (0.45 gram disodium phosphate heptahydrate), 0.01 gram potassium phosphate, and 0.2 gram sodium chloride in distilled water to make 100 milliliters.
(3) Magnetic stirrer.
(4) Stainless steel lockwasher (1.2 × 0.2 centimeters) or other suitable magnetic stirring bar.
(5) Glasss or polyethylene-coated magnetic stirring bar.
(6) Test tubes, 85 × 15 millimeters, thick-walled.
(7) Beakers, 50 milliliters.
(8) Pipettes as requried.
(9) Timer.
(10) Microscope.
(11) Incubator or waterbath (at 35° to 37° C).
(12) pH meter, equipped with glass and saturated calomel electrodes.

(c) *Minimal requirements for semen to be used for testing*—(1) *Sample collection and storage.* Specimens must not be collected in a rubber or latex sheath or condom and should be kept tightly stoppered in a tube at room temperature before being tested.
(2) *Sample age.* Not more than 4 hours old.
(3) *Density.* Not less than 50 million per milliliter.

(4) *Motility.* 40 to 50 percent of the sperm should show rapid forward motion when examined with a fresh mount at 35° to 37° C.
(5) *Visocity.* Properly liquefied semen, not "Stringy" when run out of a pipette, and appearing homogeneous to the naked eye.
(d) *Control test for the effect of dilution and mixing on sperm activity.* The following control test should be done on each specimen of semen just before it is used for the spermicidal tests. If the semen is in use for more than 2 hours, the control test should be repeated.
(1) Bring all materials to 35° to 37° C, using an incubator or waterbath.
(2) Pipette 0.2 milliliter of semen into a test tube, taking care that no semen splashes up the sides of the tube.
(3) Add a lockwasher or other magnetic stirring bar, and insert the tube in the field of the magnetic stirrer.
(4) Add 1.0 milliliter of saline, simultaneously starting the stirrer and timer. This is zero time.
(5) Let mix for 10 seconds. Place a drop on a plain slide, cover with a cover-slip, and put on the microscope stage.
(6) At 40 seconds (i.e., 30 seconds after end of mixing) rapidly examine five fields with low power (100 to 150 ×), followed by five fields with high power (400 to 600 ×).
(7) If activity in the dilution is not satisfactory in terms of the original assessment, the sampe of semen must be discarded.
(8) Add 1.0 milliliter of buffered glucose solution, mix, and reexamine for sperm activity after 30 minutes at 37° C.
(e) *Testing for spermicidal effectiveness.* Just before the test is to be done, dilutions of spermicidal products should be made up freshly with a 0.9-percent saline solution. One gram of the product is weighed into a 50-milliliter beaker, and 11.0 milliliters of normal saline are added. This solution is kept at 35° to 37° C for 15 minutes. After this period, the spermicidal solution is stirred for 15 minutes at 35° to 37° C if possible—otherwise at room temperature (22° to 25° C)—using a glass or polyethylene-coated magnetic stirrer. After this stirring, the solution is allowed to stand at 35° to 37° C for 30 minutes. Immediately before each test, the spermicidal solution is stirred 20 times, using a glass rod. The pH of the solution is recorded with a pH meter. For foaming tablets, one reading is taken while foaming is in progress, and a second reading is taken when the foam is completely exhausted.
(1) Bring all material to 35° to 37° C, using an incubator or waterbath.

(2) Place 0.2 milliliter of warm semen in a test tube, taking care that no semen splashes up the sides of the test tube because this might cause a false-fail.

(3) Add a lockwasher or other magnetic stirring bar, and insert the tube in the field of the magnetic stirrer.

(4) Add 1.0 milliliter of the warm spermicidal solution prepared as above, simultaneously starting the stirrer and timer. This is zero time.

(5) Let stir for 10 seconds. Place a drop on a plain slide, cover with a cover-slip, and put on the microscope stage.

(6) At 40 seconds examine five fields rapidly with low power (100 to 150X). If no motility is observed, confirm by examining at least five fields under high power (400 to 600X). If even a single sperm shows any sign of life, i.e., jerking or swimming, score "fail." If no sperm show any sign of life, score "preliminary pass."

(7) If no active sperms are found, add 1.0 milliliter of buffered glucose solution to the tube containing the semen-spermicide mixture. Stir well with a glass rod or mix well by drawing the fluid into a pipette and running out three times. Place in an incubator for about 30 minutes and reexamine as above. If still no active sperms are seem, score "final pass."

(f) *Test data retention.* All raw data generated as a result of this testing for every product formulation shall be retained and shall be indexed by product identification and the date of the study. The manufacturer shall permit an authorized employee of the Food and Drug Administration at a reasonable time and in a reasonable manner to inspect and copy all such records. If the manufacturer refuses to permit such inspection or fails to retain such test data, the Food and Drug Administration will take action to prohibit further marketing of the product.

(g) *Test modifications.* The formulation of certain products may require modification of this in vitro testing procedure. Any proposed modification shall be submitted with supporting documentation (preferably in quadruplicate) to the office of the Hearing Clerk (HFA–305), food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857. The Director, Division of OTC Drug Evaluation, shall notify the applicant in writing of the agency's decision regarding the requested test modification. All such requests and the agency's response shall be maintained in a permanent file for public review at the office of the Hearing Clerk.

Labeling

§ 351.50 Labeling of vaginal contraceptive drug products.

(a) The following definitions draw distinctions between various parts of the labeling.

(1) According to the definition in section 201 (m) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 (m), the term "labeling" means all labels and other written, printed, or graphic matter (e.g., package inserts) on or accompanying any article or any of its containers or wrappers.

(2) According to the definition in section 201(k) of the act, the term "label" specifically means that part of the labeling which appears on the immediate container of any article.

(3) According to the definition in § 201.60 of this chapter, the term "principal display panel" means that part of the label that is most likely to be displayed, presented, shown, or examined under customary conditions of display for retail sale.

(b) The distinctions in paragraph (a) of this section are pointed out because certain information is to be contained in specific locations within the labeling of vaginal contraceptive drug products. Accordingly, the labeling of the product contains all the information required by §§ 351.52, 351.54, and 351.56. The label of the product contains all the information required by §§ 351.52 and 351.54. And the principal display panel contains all the information required by § 351.52.

§ 351.52 Principal display panel.

(a) *Statement of identity.* The principal display panel of the product contains the established name of the drug, if any, and identifies the product as a "vaginal contraceptive."

(b) *Other information.* The principal display panel of the product contains the following additional information.

(1) "Intended for the prevention of pregnacy."

(2) When applicable, the principal display panel contains a statement that the product is to be used only with a diaphragm.

§ 351.54 Label.

The label of the product contains the information required by § 351.52 in addition to the following statements.

(a) *Warnings.* The label of the product contains the following warnings under the heading "Warnings."

(1) "Keep this and all drugs out of the reach of children."

(2) "In case of accidental ingestion, call a Poison Control Center, emergency medical facility, or a doctor."

(3) "If vaginal irritation occurs and continues, contact your physician."

(b) *Other required information.* The label of the product contains the following additional information.

(1) A statement of the active ingredient(s) and the quantity.

(2) A statement of the inactive ingredients.

(3) The storage condition of the product.

(4) An expiration date (under conditions of normal storage).

(5) Brief directions for use which include a statement setting forth the length of time which must elapse between insertion and intercourse in order to provide maximum protection against pregnancy.

§ 351.56 Labeling.

The labeling of the product contains all the information required by §§ 351.52 and 351.54 in addition to the following statements.

(a) *Directions.* The labeling of the product contains the following information under the heading "Directions," followed by "or as directed by a physician."

(1) Diagrammed instructions explaining the proper method of application (insertion).

(2) "Insert —— (jelly, cream, foam, tablet, etc.) into the vagina not less than —— (minute(s)) and not more than —— (hour(s), minute(s)) before each act of intercourse."

(3) "If this product is used together with another contraceptive method, there will probably be better protection against pregnancy."

(4) "If your physician has told you that you should not become pregnant, ask your physician if you can use this product for contraception."

(5) "If douching is desired, always wait at least 6 hours after intercourse before douching."

(6) Instructions for cleaning the applicator (if applicable).

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "indications" that is limited to one or more of the following phrases.

(1) "Vaginal contraceptive ——." Fill in the blank with the appropriate dosage form, e.g., "jelly," "foam," "tablet," "suppository," "cream."

(2) "Spermicidal."

(3) "Spermicide."

(4) "Sperm-killing."

(5) "Extra protection for women who forget to take one or more contraceptive pills."

(6) "For women who find other methods of contraception unacceptable."

(7) "Provides reliable protection against pregnancy."

(8) "Effective contraceptive alone or in the event the contraceptive pill is forgotten."

(c) *Other allowable statements.* The labeling may also contain any of the following words or phrases:

(1) "Safe."

(2) "Effective contraceptive."

(3) "Effective vaginal contraceptive."

(4) "Effective spermicide."

(5) "Highly spermicidal."

(6) "Powerful spermicide."

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding this proposal on or before March 12, 1981. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before April 13, 1981. Comments may be seen in the above-named office between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with Executive Order 12044, as amended by Executive Order 12221, the economic effects of this proposal have been carefully analyzed, and it has been determined that the proposed rulemaking does not involve major economic consequences as defined by that order. A copy of the regulatory analysis assessment supporting this determination is on file with the Hearing Clerk, Food and Drug Administration.

Dated: December 2, 1980.

Jere E. Goyan,

Commissioner of Food and Drugs.

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