

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 80N-0280]

RIN 0910-AA01

DMB  
Display Date 5-8-02  
Publication Date 5-9-02  
Certifier D. Hawkins

**Status of Certain Additional Over-the-Counter Drug Category II and III Active**

**Ingredients**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Final rule.

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**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule stating that a certain ingredient in over-the-counter (OTC) drug products is not generally recognized as safe and effective or is misbranded. FDA is issuing this final rule after considering the reports and recommendations of various OTC drug advisory review panels and public comments on proposed agency regulations. This final rule addresses the ingredient octoxynol 9, considered in the rulemaking for OTC vaginal contraceptive drug products. Based on the failure of interested parties to submit new data or information to FDA under the proposed regulation, the agency has determined that the presence of this active ingredient in an OTC drug product would result in that drug product not being generally recognized as safe and effective for its intended use or would result in misbranding. This final rule is part of FDA's ongoing OTC drug product review.

**DATES:** This regulation is effective [*insert date 180 days after date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:** Helen Cothran, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

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**SUPPLEMENTARY INFORMATION:****I. Background**

In the **Federal Register** of November 7, 1990 (55 FR 46914), FDA published under § 330.10(a)(7)(ii) (21 CFR 330.10(a)(7)(ii)) a final rule on the status of certain OTC drug Category II and III active ingredients. That final rule declared as not generally recognized as safe and effective certain active ingredients that had been proposed as nonmonograph (Category II or III) under the agency's OTC drug review. The periods for submission of comments and new data following the publication of a notice of proposed rulemaking had closed and no significant comments or new data had been submitted to upgrade the status of these ingredients. In each instance, a final rule for the class of ingredients involved had not been published to date.

In the **Federal Register** of May 10, 1993 (58 FR 27636), FDA published a final rule establishing that certain additional active ingredients in OTC drug products are not generally recognized as safe and effective or are misbranded. That final rule included active ingredients from a number of OTC drug rulemakings that were not covered by the November 7, 1990, final rule (see table I of the May 10, 1993, final rule (58 FR 27636 at 27639 to 27641) for a list of OTC drug rulemakings and active ingredients covered by that final rule).

In the proposed rulemaking for OTC vaginal contraceptive drug products (45 FR 82014, December 12, 1980), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (the Panel) placed nonoxynol 9 and octoxynol 9 in Category I (safe and effective), placed phenylmercuric acetate, phenylmercuric nitrate, and other compounds containing mercury in Category II for safety, and placed dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate), laureth 10S, and methoxypolyoxyethylene glycol 550 laurate in Category III for efficacy. In the preamble to the Panel's report (45 FR 82014), the agency stated that clinical trials of each product or final formulation may be the only certain predictor of its effectiveness in humans. The agency further stated that if clinical trials are necessary, manufacturers may be required to submit a new drug application (NDA) or supplement an existing NDA. The agency stated that

stated that it would announce its decision in a separate **Federal Register** document or in the tentative final order.

In the proposed rule for OTC vaginal contraceptive drug products (60 FR 6892, February 3, 1995), the agency proposed that manufacturers of OTC vaginal contraceptive drug products obtain approved applications for marketing of their products. The agency took this action because the evidence currently available shows that effectiveness of these products is dependent upon the final formulation and clinical studies in humans are needed to establish the effectiveness of the active ingredients in OTC vaginal contraceptive drug products. Therefore, each product must be tested in appropriate clinical trials under actual conditions of use. FDA encouraged manufacturers to consult with the agency regarding testing and the submission of applications as soon as possible. In the proposed rule, all of the ingredients evaluated by the Panel were considered nonmonograph for reasons of safety and/or effectiveness.

In response to this proposed rule, the agency received no comments or data relating to the safety and effectiveness of any of the Panel's Category II or III ingredients. Therefore, in the **Federal Register** of April 22, 1998 (63 FR 19799), the agency issued a final rule regarding the nonmonograph status of these Category II and III ingredients. Based on the absence of substantive comments in opposition to the agency's proposed nonmonograph status for these ingredients, as well as the failure of interested parties to submit new data or information to FDA under the regulation, the agency determined that the presence of these ingredients in an OTC drug product would result in the drug product not being generally recognized as safe and effective or would result in misbranding.

In response to the proposed rule, the agency was informed of ongoing clinical trials involving nonoxynol 9 (Refs. 1, 2, and 3). However, the agency is not aware of any clinical trials, nor have any comments or data on octoxynol 9 been submitted to the agency since the proposed rule. Accordingly, FDA concludes that octoxynol 9 has not been shown to be generally recognized as safe and effective for its intended use as a vaginal contraceptive and should be eliminated from

OTC drug products 6 months after the publication of this final rule in the **Federal Register**, regardless of whether further testing is undertaken to justify future use. Publication of this final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of a NDA that may provide for prescription or OTC marketing status (see part 314 (21 CFR part 314)).

The monograph or new drug status of nonoxynol 9 will be addressed after completion and analysis of the ongoing clinical trials. This final rule for octoxynol 9 does not affect the current marketing status of nonoxynol 9 as an OTC vaginal contraceptive.

## **II. The Agency's Final Conclusions on Certain OTC Drug Category II and III Ingredients**

For the reasons discussed in section I of this document, the agency has determined that octoxynol 9 should be deemed not generally recognized as safe and effective for OTC use before a final rule is established for OTC vaginal contraceptive drug products. Accordingly, any drug product containing octoxynol 9 and labeled for OTC use as a vaginal contraceptive or spermicide will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations is required for marketing. This applies to any OTC drug product containing octoxynol 9 and labeled for use as a vaginal contraceptive or vaginal spermicide that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule. Further, any OTC drug product that was previously initially introduced or initially delivered for introduction into interstate commerce cannot be repackaged or relabeled after the effective date of the rule. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

### III. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency concludes that this final rule is consistent with the principles set out in the Executive order and in these two statutes. Further, since this final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation, FDA need not prepare additional analyses under the Unfunded Mandates Reform Act.

The purpose of this final rule is to finalize the proposed nonmonograph status of octoxynol 9 in order to expedite completion of the OTC drug review. There are a limited number of products currently marketed that will be affected by this rule. The agency's Drug Listing System identifies two manufacturers of OTC vaginal contraceptive drug products containing octoxynol 9, although there may be some additional products that are not currently included in the agency's system. One manufacturer markets four products and the other manufacturer markets one product, for a total of five products. At least one of the manufacturers is considered a small entity, using the U.S. Small Business Administration designation for this industry (750 employees).

Manufacturers of these products will no longer be able to market products containing octoxynol 9 after the effective date of this final rule. One of the manufacturers of octoxynol 9 also produces products that contain nonoxynol 9, which is currently being tested in clinical trials. Other manufacturers will be able to reformulate vaginal contraceptive drug products that contain octoxynol 9 and continue to market them with nonoxynol 9, pending completion of the final rule for these products. The agency estimates the cost of reformulation and relabeling to range from \$100,000 to \$500,000 per product. Using the midpoint of the cost estimate implies total costs up to \$1.5 million. However, the agency believes the total costs will be smaller because all currently marketed products may not be reformulated. The manufacturers have known since the publication of the proposed rule in the **Federal Register** of February 3, 1995, that if adequate data from clinical trials were not submitted to support safety and effectiveness, cessation of marketing of the current products would be required when the final rule is published. Generally, when safety is not a concern, manufacturers will continue to market products that they know will become nonmonograph for as long as legally possible to maximize their profits for that product line.

The agency considered but rejected not acting on this ingredient in advance of the completion of the final rule on OTC vaginal contraceptive drug products. The ongoing clinical trials involving nonoxynol 9 are not expected to be completed for a period of time. However, safety and effectiveness have not been established for octoxynol 9 and no testing is currently being done. Therefore, the agency concludes that consumers will benefit from the early removal from the marketplace of products containing octoxynol 9.

Because so few small firms will be affected, the agency certifies that there will not be a significant economic impact on a substantial number of small firms.

#### **IV. Paperwork Reduction Act of 1995**

This final rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

## **V. Environmental Impact**

The agency has determined under 21 CFR 25.31(a) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

## **VI. Federalism**

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

## **VII. References**

The following references are on display in the Dockets Management Branch (address above) under Docket No. 80N-0280 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. FDA, Transcript of Joint Meeting of the Nonprescription Drugs, Reproductive Health Drugs, Anti-Infective Drugs and Antiviral Drugs Advisory Committees, November 22, 1996, pp. 86-99, in OTC Vol. 11ATFM2.
2. Letter from D. L. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET 6.
3. Letter from D. L. Bowen, FDA, to R. W. Soller, Nonprescription Drug Manufacturers Association, coded LET 7.

**List of Subjects in 21 CFR Part 310**

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

**PART 310—NEW DRUGS**

1. The authority citation for 21 CFR part 310 continues to read as follows:

**Authority:** 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

2. Section 310.545 is amended by adding a paragraph heading (a)(28)(i) after the existing paragraph heading, by adding paragraphs (a)(28)(ii) and (d)(36), by revising paragraph (d)(28), and by adding and reserving paragraphs (d)(34) and (d)(35) to read as follows:

**§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.**

(a) \* \* \*

(28) *Vaginal contraceptive drug products—(i) Approved as of October 22, 1998.* \* \* \*

(ii) *Approved as of [insert date 180 days after date of publication in the Federal Register].*

Octoxynol 9

\* \* \* \* \*

(d) \* \* \*

(28) October 22, 1998, for products subject to paragraphs (a)(27) and (a)(28)(i) of this section.

\* \* \* \* \*

(34) [Reserved]

(35) [Reserved]

(36) [Insert date 180 days after date of publication in the **Federal Register**], for products subject to paragraph (a)(28)(ii) of this section.

Dated: 4/29/02  
April 29, 2002.



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Margaret M. Dotzel,  
Associate Commissioner for Policy.

[FR Doc. 02-????? Filed ??-??-02; 8:45 am]

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*Dawn P. Hawkins*