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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 310

**[Docket Nos. 75N–183F, 75N–183D, and 80N–0280]**

**RIN 0910–AA01**

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

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

**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a final rule stating that certain ingredients in over-the-counter (OTC) drug products are not generally recognized as safe and effective or are 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, which were issued in the form of a tentative final monograph (proposed rule). 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 has determined that the presence of these ingredients in an OTC drug product would result in that drug product not being generally recognized as safe and effective or would result in misbranding. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

**DATES:** Effective October 19, 1998.

**FOR FURTHER INFORMATION CONTACT:** Gerald M. Rachanow, Center for Drug Evaluation and Research (HFD–560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2307.

**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 Category 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 (NPRM) 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 (58 FR 27636 at 27639 to 27641) for a list of OTC drug rulemakings and active ingredients covered by that final rule.)

At that time, there were other OTC drug review rulemakings for which the period for submission of comments and/or new data was still pending. Those periods have now closed, and there are a number of active ingredients for which no significant comments or new data were submitted. In each instance, a final rule for the class of ingredients involved has not been published to date. This final rule addresses some of the Category II and Category III active ingredients in those classes of ingredients, specifically active ingredients considered in the rulemakings for OTC vaginal contraceptive, first aid antiseptic, and antimicrobial diaper rash drug products.

In the advance notice of proposed rulemaking (ANPRM) for OTC vaginal contraceptive drug products (45 FR 82014, December 12, 1980), the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products placed phenylmercuric acetate and phenylmercuric nitrate in Category II for safety and placed dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate), laureth 10S, and methoxypolyoxyethyleneglycol 550 laurate in Category III for efficacy. In the tentative final monograph (TFM) for OTC vaginal contraceptive drug products (60 FR 6892, February 3, 1995), the agency proposed that all of these ingredients be nonmonograph. In response to this TFM (NPRM), the agency received no comments or data relating to the safety and effectiveness of these ingredients.

In the ANPRM for mercury-containing drug products for OTC topical antimicrobial use (47 FR 436, January 5, 1982), the Advisory Review Panel on OTC Miscellaneous External Drug Products placed all mercury compounds in Category II for topical antimicrobial use. This included the following ingredients: Ammoniated mercury; calomel (mercurous chloride); merbromin (mercurochrome); mercuric chloride (bichloride of mercury, mercury chloride); mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride); mercuric salicylate; mercuric sulfide (red mercuric sulfide); mercuric oxide, yellow; mercury; mercury chloride; mercury oleate; nitromersol; para-chloromercuriphenol; phenylmercuric nitrate; thimerosal; vitromersol; and zyloxin. In the NPRM for OTC first aid antiseptic drug products (56 FR 33644, July 22, 1991), the agency proposed that all of these ingredients were either Category II or Category III. In response to this NPRM, the agency received no comments or data relating to the safety and effectiveness of these ingredients.

In an amendment to the proposed rulemaking for OTC topical antimicrobial drug products (55 FR 25246, June 20, 1990), the agency proposed that p-chloromercuriphenol and all other ingredients containing mercury were Category II for the treatment and prevention of diaper rash. In response to this NPRM, the agency received no comments or data relating to the safety and effectiveness of these ingredients.

### II. Affected Rulemakings and Category II and III Ingredients

Table I of this document lists the titles and docket numbers of the specific rulemakings containing active ingredients that are addressed in this document, together with the publication dates of the ANPRM and the NPRM, as well as the closing dates for comments and submission of new data for each rulemaking. FDA advises that the active ingredients discussed in this document (see Table II of section II of this document) will not be included in the relevant final monographs because they have not been shown to be generally recognized as safe and effective for their intended use. The agency further advises that these ingredients should be eliminated from OTC drug products 6 months after the date of publication in the **Federal Register** of this final rule regardless of whether further testing is undertaken to justify future use.

The agency points out that publication of a 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 new drug application that may provide for prescription or OTC marketing status. (See part 314 (21 CFR part 314).) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to amend or establish a monograph, as appropriate. (See § 10.30 (21 CFR 10.30).)

TABLE I.—OTC DRUG RULEMAKINGS COVERED BY THIS FINAL RULE

| Rulemaking and action | Publication date | Comment closing date | New data closing date |
|---|---|---|---|
| (1) *Vaginal contraceptive drug products* (Docket No. 80N–0280) | | | |
| Advance notice of proposed rulemaking (ANPRM) | December 12, 1980 | March 12, 1981 | Not applicable (N/A) |
| Notice of proposed rulemaking (NPRM) | February 3, 1995 | June 5, 1995 | February 5, 1996 |
| (2) *First aid antiseptic drug products* (Docket No. 75N–0183) | | | |
| ANPRM | January 5, 1982 | April 5, 1982 | N/A |
| (Docket No. 75N–183F) | | | |
| NPRM | July 22, 1991 | January 2, 1992 | July 22, 1992 |
| (3) *Antimicrobial diaper rash drug products* (Docket No. 75N–0183) | | | |
| ANPRM | September 7, 1982 | December 6, 1982 | January 5, 1983 |
| (Docket No. 75N–183D) | | | |
| NPRM | June 20, 1990 | December 17, 1990 | June 20, 1991 |

Based on the criteria discussed above, FDA concludes that the following ingredients are not generally recognized as safe and effective and are misbranded when labeled as OTC drugs for the following uses:

TABLE II.—INGREDIENTS COVERED BY THIS FINAL RULE

| Rulemaking and ingredients | Ingredient classification | |
|---|---|---|
| | Advance notice of proposed rulemaking | Notice of proposed rulemaking |
| (1) *First aid antiseptic drug products*: (Docket No. 75N–183F) | | |
| Ammoniated mercury | II | II |
| Calomel (mercurous chloride) | II | III |
| Merbromin (mercurochrome) | II | III |
| Mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride) | II | III |
| Mercuric chloride (bichloride of mercury, mercury chloride) | II | II |
| Mercuric oxide, yellow | II | II |
| Mercuric salicylate | II | II |
| Mercuric sulfide, red | II | II |
| Mercury | II | II |
| Mercury oleate | II | II |
| Mercury sulfide | II | II |
| Nitromersol | II | II |
| Para-chloromercuriphenol | II | II |
| Phenylmercuric nitrate | II | III |
| Thimerosal | II | II |
| Vitromersol | II | II |
| Zyloxin | II | II |
| (2) *Vaginal contraceptive drug products*: (Docket No. 80N–0280) | | |
| Dodecaethylene glycol monolaurate) (polyethylene glycol 600 monolaurate) . | III | III |
| Laureth 10S | III | III |
| Methoxypolyoxyethyleneglycol 550 laurate | III | III |
| Phenylmercuric acetate | II | II |
| Phenylmercuric nitrate | II | II |
| (3) *Antimicrobial diaper rash drug products*: (Docket No. 75N–183D) | | |
| Para-chloromercuriphenol | NA | II |
| Any other ingredient containing mercury | NA | II |

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

No substantive comments or additional data have been submitted to the OTC drug review to support any of the ingredients listed in Table II of this document as being generally recognized as safe and effective for the specified OTC uses. The agency has determined that these ingredients should be deemed not generally recognized as safe and effective for OTC use before a final monograph for each respective drug category is established. Accordingly, any drug product containing any of these ingredients and labeled for the OTC use identified in Table II of this document 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. As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to amend the appropriate monograph to include any of the above ingredients in OTC drug products in Table II of this document. (See § 10.30.) Any OTC drug product containing any of the ingredients in Table II of this document and labeled for the use identified in Table II of this document initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not the subject of an approved application will be in violation of sections 502 and 505 of the act and, therefore, subject to regulatory action. Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the effective date of the rule would be required to be in compliance with the rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

### IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). 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 significant regulatory options that would minimize any significant impact of the rule on small entities.

Title II of the Unfunded Mandates Reform Act (2 U.S.C. 1501 *et seq.*) requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The agency believes that this final rule is consistent with the principles set out in the Executive Order and in these two statutes. The purpose of this final rule is to act on the proposed nonmonograph status of certain ingredients in advance of finalization of other monograph conditions 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. Of the 17 mercury active ingredients included in the final rule, the agency is aware of 12 OTC drug products containing merbromin, 1 product containing phenylmercuric nitrate, and 7 products containing thimerosal. These products are marketed by eight different manufacturers, most of which are considered small entities, using the U.S. Small Business Administration designation for this industry (750 employees). The agency is not aware of any topical antimicrobial diaper rash or vaginal contraceptive drug products containing any of the active ingredients included in this final rule.

Manufacturers of these products will no longer be able to market products containing the ingredients included in this final rule after its effective date. While the manufacturers will incur a loss of revenue for these products, the agency believes the economic impact will be minimal for several reasons. A. C. Nielsen (Nielsen), a recognized provider of market research business information and analysis, maintains product data from a sample of 4,000 retail outlets selected to represent the geographical and retail characteristics of the U.S. OTC market. Based on these Nielsen data, the agency estimates that total sales for these products represent less than 0.1 percent of all sales of OTC first aid drug products. For the affected companies, these product sales comprised less than 1 percent of OTC drug revenues. The industry has been aware of the status of these products since 1982, and all of the manufacturers identified by FDA also produce products containing ingredients proposed for inclusion in the monograph. The lost sales from the nonmonograph products are expected to be offset by increased sales of the substitute products.

The agency considered, but rejected, not acting on these ingredients in advance of the finalization of other monograph conditions. The final monographs for OTC topical antimicrobial and vaginal contraceptive drug products are not expected to be completed for a period of time. The agency also considered publishing an additional notice specifying that the determinations on the ingredients in this final rule would be included in a final rule prior to publication of a final rule including the determinations on ingredients for which new data and information have been submitted. However, safety and effectiveness have not been established for the ingredients included in this current final rule and manufacturers have not submitted the necessary data in response to earlier opportunities. The agency's experience has been that under these circumstances companies have not submitted data in response to yet another opportunity. Consumers will benefit from the early removal from the marketplace of products containing ingredients for which safety and effectiveness have not been established. Consumers can then purchase products containing only ingredients proposed for monograph status. Manufacturers who choose to reformulate or replace affected products will be able to use alternative ingredients that are proposed as monograph conditions without incurring any additional expense of clinical testing for those ingredients. As noted previously, FDA believes that most manufacturers currently produce such products.

While this final rule may cause manufacturers to discontinue marketing or to reformulate some products prior to issuance of the applicable final monograph, these manufacturers have known for some time that if adequate data were not submitted to support safety and effectiveness, cessation of marketing of the current products would be required, in any event, when the final monographs are published. Because this rule imposes no additional reporting or recordkeeping requirements, no additional professional skills are necessary to comply.

The analysis shows that this final rule is not economically significant under Executive Order 12866 and that the agency has considered the burden to small entities. Based on the above analysis, the agency does not believe that the majority of manufacturers will incur a significant economic impact. However, there may be a few that could incur significant reformulation costs or inventory losses. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act. Finally, this analysis shows that the Unfunded Mandates Reform Act does not apply to the final rule because it would not result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million.

### V. Environmental Impact

The agency has determined under 21 CFR 25.31(c) 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.

### 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, 356, 357, 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 paragraphs (a)(27) and (a)(28), by revising paragraph (d) introductory text, by reserving paragraphs (d)(26) and (d)(27), and by adding paragraph (d)(28) to read as follows:

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

(a) * * *

(27) *Topical antimicrobial drug products*—(i) *First aid antiseptic drug products.*

Ammoniated mercury
Calomel (mercurous chloride)
Merbromin (mercurochrome)
Mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride)
Mercuric chloride (bichloride of mercury, mercury chloride)
Mercuric oxide, yellow
Mercuric salicylate
Mercuric sulfide, red
Mercury
Mercury oleate
Mercury sulfide
Nitromersol
Para-chloromercuriphenol
Phenylmercuric nitrate
Thimerosal
Vitromersol
Zyloxin

(ii) *Diaper rash drug products.*

Para-chloromercuriphenol
Any other ingredient containing mercury

(28) *Vaginal contraceptive drug products.*

Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate)
Laureth 10S
Methoxypolyoxyethyleneglycol 550 laurate
Phenylmercuric acetate
Phenylmercuric nitrate
Any other ingredient containing mercury

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction to interstate commerce after the dates specified in paragraphs (d)(1) through (d)(28) of this section.

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

Dated: April 8, 1998.

**William K. Hubbard,**

*Associate Commissioner for Policy Coordination.*

[FR Doc. 98–10578 Filed 4–21–98; 8:45 am]

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## DEPARTMENT OF THE INTERIOR

## Office of Surface Mining Reclamation and Enforcement

## 30 CFR Part 938

**[PA–112–FOR]**

## Pennsylvania Regulatory Program

**AGENCY:** Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

**ACTION:** Final rule; approval of amendments.

**SUMMARY:** OSM is approving, with certain exceptions, a proposed amendment to the Pennsylvania permanent regulatory program (hereinafter referred to as the Pennsylvania program) under the Surface Mining Control and Reclamation Act of 1977 (SMCRA). The amendment revises the Pennsylvania program to incorporate changes made by Pennsylvania House Bill 1075 and subsequent Pennsylvania law Act 1994–114. The amendment is intended to provide special authorization for coal refuse disposal in areas previously affected by mining which contain pollutional discharges.

**EFFECTIVE DATE:** April 22, 1998.

**FOR FURTHER INFORMATION CONTACT:** Robert J. Biggi, Director, Office of Surface Mining Reclamation and Enforcement, Harrisburg Field Office, Harrisburg Transportation Center, Third Floor, Suite 3C, 4th and Market Streets, Harrisburg, Pennsylvania 17101, Telephone: (717) 782–4036.

**SUPPLEMENTARY INFORMATION:**



### I. Background on the Pennsylvania Program

On July 31, 1982, the Secretary of the Interior conditionally approved the Pennsylvania program. Background information on the Pennsylvania program including the Secretary's findings, the disposition of comments, and a detailed explanation of the conditions of approval of the Pennsylvania program can be found in the July 30, 1982, **Federal Register** (47 FR 33050). Subsequent actions concerning the conditions of approval and program amendments are identified at 30 CFR 938.11, 938.12, 938.15 and 938.16.

### II. Submission of the Amendment

By letter dated September 14, 1995 (Administrative Record Number PA 837.01), Pennsylvania submitted an amendment to the Pennsylvania program. The amending language is contained in Pennsylvania House Bill 1075 and was enacted into Pennsylvania law as Act 1994–124. The amendments change Pennsylvania's Coal Refuse Disposal Act (of September 24, 1968 (P.L. 1040, No. 318) and amended on October 10, 1980 (P.L. 807, No. 154)) to provide for authorization for refuse disposal in areas previously affected by mining which contain pollutional