

(16) When should a clinical investigation be considered "completed?" How soon after a clinical investigation is completed should the results be disclosed?

(17) How can we assure timely disclosure of study results after completion of a study?

#### *Public Discussion of Emergency Research*

Currently, all emergency research protocols are subject to IRB review and community consultation. FDA has received some suggestions that it may be important, at least in some cases, to have additional public discussion, such as during an open meeting of an advisory committee or other expert panel. We invite comment on the following questions. Is there a need for such additional review and public discussion? If so, what criteria would be used to determine which protocols should be subject to this additional review and discussion?

(18) What type of venue would be best for this additional review and public discussion?

(19) What information should be included in this review?

#### *Additional Challenges*

(20) Are there any additional challenges to the conduct of emergency research that have not been identified in the preceding questions?

(21) If so, what are they and how should they be addressed?

### **VI. Notice of Hearing Under 21 CFR Part 15**

The Acting Commissioner of Food and Drugs (the Acting Commissioner) is announcing that the public hearing will be held in accordance with part 15. The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, the Office of Policy, and the Office of Human Research Protection.

Persons who wish to participate in the part 15 hearing must file a written or electronic submission with the Division of Dockets Management (see **ADDRESSES** and **DATES**). To ensure timely handling, any outer envelope should be clearly marked with the docket number found in brackets in the heading of this document, along with the statement "Emergency Research." Requests to make a presentation should contain the potential presenter's name; address; telephone number; affiliation, if any; the sponsor of the presentation (e.g., the organization paying travel expenses or

fees), if any; a brief summary of the presentation (including the discussion questions identified by number that will be addressed).

Under § 15.30(f), the hearing is informal, and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members may question any person during or at the conclusion of each presentation.

Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (part 10 (21 CFR part 10, subpart C)). Under § 10.205, representatives of the electronic media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants.

To the extent that the conditions for the hearing, as described in this document, conflict with any provisions set out in part 15, this document acts as a waiver of those provisions as specified in § 15.30(h).

### **VII. Request for Comments**

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic notices of participation and comments for consideration at the hearing. To permit time for all interested persons to submit data, information, or views on this subject, the administrative record of the hearing will remain open for 45 days following the hearing. Persons who wish to provide additional materials for consideration should file these materials with the Division of Dockets Management (see **ADDRESSES**). You should annotate and organize your comments to identify the specific questions identified by number to which they refer (see section V of this document). Two paper copies of any mailed comments are to be submitted, except that individuals may submit one paper copy. Comments are to be identified with the docket number at the heading of this document. Received comments may be seen in Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

### **VIII. Transcripts**

The hearing will be transcribed as stipulated in § 15.30(b). Transcripts of the hearing will be available for review at the Division of Dockets Management (see **ADDRESSES**) and on the Internet at <http://www.fda.gov/ohrms/dockets> approximately 21 days after the hearing.

You may place orders for copies of the transcript at the meeting or through the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, rm. 6-30, Rockville, MD 20857, at a cost of 10 cents per page.

Dated: August 18, 2006.

**Jeffrey Shuren,**

*Associate Commissioner for Policy.*

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## **DEPARTMENT OF HEALTH AND HUMAN SERVICES**

### **Food and Drug Administration**

#### **21 CFR Part 310**

[Docket No. 1978N-0065 (formerly Docket No. 78N-0065)]

RIN 0910-AF53

#### **Skin Bleaching Drug Products For Over-the-Counter Human Use; Proposed Rule**

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

**ACTION:** Proposed rule; withdrawal of previous proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would establish that over-the-counter (OTC) skin bleaching drug products are not generally recognized as safe and effective (GRASE) and are misbranded. FDA is also withdrawing the previous proposed rule on skin bleaching drug products for OTC human use, which was issued in the form of a tentative final monograph (TFM). FDA is issuing this proposed rule after considering new data and information on the safety of hydroquinone, the only active ingredient that had been proposed for inclusion in a monograph for these products. This proposal is part of FDA's ongoing review of OTC drug products. Further, upon issuance of a final rule, FDA intends to consider all skin bleaching drug products, whether currently marketed on a prescription or OTC basis, to be new drugs requiring an approved new drug application (NDA) for continued marketing.

**DATES:** Submit written or electronic comments by December 27, 2006; submit written or electronic comments on FDA's economic impact determination by December 27, 2006. The September 3, 1982, proposed rule (47 FR 39108) is withdrawn as of August 29, 2006. See section IX for the proposed effective date of any final rule that may publish based on this proposal.

**ADDRESSES:** You may submit comments, identified by Docket No. 1978N-0065 and RIN number 0910-AF53, by any of the following methods:

*Electronic Submissions*

Submit electronic comments in the following ways:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.
- Agency Web site: <http://www.fda.gov/dockets/ecomments>.

Follow the instructions for submitting comments on the agency Web site.

*Written Submissions*

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier [For paper, disk, or CD-ROM submissions]: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

To ensure more timely processing of comments, FDA is no longer accepting comments submitted to the agency by e-mail. FDA encourages you to continue to submit electronic comments by using the Federal eRulemaking Portal or the agency Web site, as described in the *Electronic Submissions* portion of this paragraph.

*Instructions:* All submissions received must include the agency name and Docket No(s), and Regulatory Information Number (RIN) (if a RIN number has been assigned) for this rulemaking. All comments received may be posted without change to <http://www.fda.gov/ohrms/dockets/default.htm>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the **SUPPLEMENTARY INFORMATION** section of this document.

*Docket:* For access to the docket to read background documents or comments received, go to <http://www.fda.gov/ohrms/dockets/default.htm> and insert the docket number(s), found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Michelle M. Jackson, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, rm. 5486, Silver Spring, MD 20993-0002, 301-796-0923.

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**I. Background**

In the **Federal Register** of November 3, 1978 (43 FR 51546), FDA published an advance notice of proposed rulemaking to establish a monograph for OTC skin bleaching drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. The data and information considered by the Panel were put on display in the Division of Dockets Management (see **ADDRESSES**).

FDA's TFM for OTC skin bleaching drug products was published in the **Federal Register** of September 3, 1982 (47 FR 39108). In that TFM, FDA proposed that hydroquinone (1.5 to 2.0 percent) be GRASE as an active ingredient in OTC skin bleaching drug products. Six manufacturers, one cosmetic manufacturers' association, and one drug manufacturers' association submitted comments in response to the 1982 TFM. These comments and additional information that has come to FDA's attention since publication of the 1982 TFM are also on public display in the Division of Dockets Management (see **ADDRESSES**).

FDA is now proposing a rule that would classify OTC skin bleaching drug products as not GRASE, misbranded, and new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). This proposed rule would amend part 310 (21 CFR part 310), subpart E by adding new § 310.545(a)(17)(ii). Accordingly, the proposed monograph that published in the **Federal Register** of September 3, 1982, which would have added hydroquinone as a GRASE skin bleaching agent (part 358 (21 CFR part 358)), is withdrawn (see **DATES**).

If this proposal becomes a final rule, FDA advises that the conditions under which the drug products that are subject to this rule are not GRASE and are

misbranded (nonmonograph conditions) will be effective 30 days after the date of publication of the final rule in the **Federal Register**. On or after that date, no OTC drug product that is subject to the rule may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the final rule must be in compliance with the final rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce.

The comments to the TFM were primarily labeling comments related to skin bleaching drug products being GRASE. Because FDA is proposing in this current notice that there are no GRASE skin bleaching drug products, discussion of the submitted comments is unnecessary at this time. Instead, FDA is only discussing the new data that are the basis for the current proposal.

**II. New Data**

A significant amount of research has been conducted on the skin bleaching ingredient hydroquinone, and a number of reports have appeared in the literature since publication of the TFM in 1982. As a result, FDA has evaluated significant additional new data on the safety of hydroquinone. Toxicology and carcinogenesis studies on orally administered hydroquinone conducted under the support of the National Toxicology Program (NTP) (Refs. 1 and 2) have indicated "some evidence" of carcinogenicity in male and female rats and in female mice. FDA's Center for Drug Evaluation and Research (CDER) Carcinogenicity Assessment Committee (CAC) has evaluated the design, results, and NTP interpretation of these studies, and concurs with the NTP's assessment. The CAC determined that additional safety studies are needed and, to date, those studies have not been submitted to FDA. Based on the evidence of carcinogenicity in animals, FDA cannot rule out the potential carcinogenic risk from topically applied hydroquinone in humans. In addition, hydroquinone has been shown to cause disfiguring effects (ochronosis) after use of concentrations as low as 1 to 2-percent.

*A. Fertility Studies*

The Environmental Protection Agency (EPA) has been evaluating the safety of hydroquinone since 1979. In the **Federal Register** of December 7, 1979 (44 FR 70664), the Interagency Testing Committee (ITC), in its Fifth Report,

designated hydroquinone for priority consideration. The ITC recommended that hydroquinone be considered for testing for carcinogenicity and teratogenicity, and that epidemiology, human metabolism, and environmental fate studies also be considered. Under section 4(a) of the Toxic Substances Control Act (15 U.S.C. 2603), EPA published two notices for manufacturers and processors of hydroquinone to perform studies to evaluate hydroquinone's: (1) Toxicokinetics and (2) potential nervous system, reproductive, and teratogenic effects. EPA did not propose oncogenicity testing of hydroquinone because the NTP was conducting a 2-year bioassay on hydroquinone. EPA's proposal was published in the **Federal Register** of January 4, 1984 (49 FR 438), and its final rule for hydroquinone testing requirements was published in the **Federal Register** of December 30, 1985 (50 FR 53145).

EPA stated in its final rule (50 FR 53145 at 53148) (references omitted): "Developmental toxicity and reproductive effects. At oral doses of 50 mg/kg/day [milligram/kilogram/day] and higher, Raczy reported that hydroquinone prolonged the diestrus period of the sexual cycle in female albino rats. Skalka, subcutaneously injecting male rats at a dose of 100 mg/kg/day for 51 days, reported decreased weights in testes, epididymides, seminal vesicles and adrenal glands; histological changes in testes indicating disrupted spermiogenesis; and diminished DNA content of sperm heads. \* \* \*"

EPA provided FDA copies of several studies (Refs. 1 through 9) that had been submitted to EPA by the Chemical Manufacturers Association (CMA). These studies addressed the evaluation guidelines outlined in EPA's final rule for hydroquinone testing requirements. The data included the 2-year bioassay study of hydroquinone that was conducted by NTP. FDA has evaluated the data on hydroquinone provided by EPA, along with other new data submitted to FDA and found the following:

In a study by Salzgeber (Ref. 3), hydroquinone was shown to inhibit the normal growth of ovaries from 10-day chick embryos cultured in vitro. Seven of the 15 ovaries were abnormal when examined histologically. The cortex was partially or totally inhibited. Only a medullary region remained, and it was poorly differentiated.

Hydroquinone increased the resorption (pregnant rats reabsorbing their fetus as a marker for unsuccessful pregnancy) rate when given in the diet to pregnant rats (Ref. 4). One hundred

percent of all hydroquinone-treated litters had resorptions, compared with 40.8 percent for control litters; 26.8 percent of implantations resulted in resorptions in treated animals compared with 10.6 percent in control rats. In a developmental toxicity study submitted by CMA (Ref. 5), hydroquinone given orally at doses of 30, 100, and 300 milligrams (mg)/kilograms (kg) to pregnant rats did not produce embryotoxic, fetotoxic, or teratogenic effects. Measurement of resorption rate was not reported in the study. Maternal toxicity was observed in the form of a slight, but statistically significant, reduction in maternal body weight gain and feed consumption in rats receiving the high dose (300 mg/kg).

In a similar protocol, the embryotoxic, fetotoxic, and teratogenic potential of hydroquinone was evaluated in pregnant rabbits (Ref. 6). Hydroquinone was dissolved in degassed distilled water and administered by gastric intubation. A dose level of 25 mg/kg/day was without maternal toxic effects and was not considered to be embryotoxic, fetotoxic, or teratogenic. In the mid-dose group (75 mg/kg/day), the only maternal toxic effect seen was a statistically significant reduction (when compared to controls) in food consumption on days 11 and 12 of gestation. In the high dose group (150 mg/kg/day), maternal toxicity was evident from the following statistically significant differences from the control data:

- Lower weights for days 16 and 18 of gestation
- Greater magnitude of weight loss over the treatment interval for days 6 to 18 of gestation
- Reduced food consumption for days 6 to 14 and 17 of gestation.

An increase in incidence of fetuses with external, visceral, and skeletal malformations was seen in the high dose group, and the incidence of litters containing affected fetuses was also increased. These incidences did not differ statistically from the controls, and malformations seen were considered to be associated with the maternal toxicity evident at the same dose level.

A reproduction study in rats was designed to assess the long-term effects of hydroquinone administered daily in an aqueous solution via gastric intubation at dose levels of 15, 50, and 150 mg/kg/day through two consecutive generations of rats (Ref. 7). The results showed that hydroquinone did not adversely affect the following:

- Maternal body weights (gestation/lactation periods)
- Gestational feed consumption
- Reproductive performance

- Fertility of parental animals
- Body weight or feed consumption during pre-mating treatment periods.

No adverse effects of treatment were evident during either generation on pup body weight, pup sex distribution, or pup survival to weaning, including doses of hydroquinone as high as 150 mg/kg/day.

Because some studies showed fertility was impaired and others did not, FDA cannot make a final determination on hydroquinone's potential to impair fertility related to decreased spermatogenesis or prolonged reproductive cycle in animals or humans. Additional studies are needed to make a better assessment.

#### B. Toxicokinetic Studies

Toxicokinetic studies with hydroquinone were conducted in rats following oral gavage and dermal administration (Ref. 8). Elimination (87 to 92-percent) of a single oral dose of hydroquinone occurred primarily within the first 8 hours after dosing. Using the cumulative 48 to 72 hour urine recovery data, dermal absorption was estimated to be 10.5 to 11.5 percent. All groups had similar chemical profiles following oral and dermal administration of hydroquinone.

Hydroquinone (2-percent) in an alcoholic vehicle was found to penetrate readily in human forehead skin following a single topical exposure in vivo for a 24-hour duration (Ref. 9). The average percutaneous absorption of hydroquinone was 57 percent. The addition of azone (a penetration enhancer) increased the absorption to 66 percent. Addition of Escalol 507 (a sunscreen), with and without azone, decreased the absorption of hydroquinone (35 and 26 percent, respectively).

#### C. Carcinogenicity Studies

The NTP 2-year bioassay studies (Refs. 1 and 2) were conducted by administering 0, 25, or 50 mg/kg hydroquinone in deionized water by gavage to groups of 65 Fischer 344/N rats of each sex, 5 days per week. Groups of 65 B6C3F1 mice of each sex were administered 0, 50, or 100 mg/kg on the same schedule. Nearly all male rats and most female rats in all vehicle control and dosed groups had nephropathy. The severity of this disease was greater in the high dose male rat group. Hyperplasia of the renal pelvic transitional epithelium and renal cortical cysts, changes which are observed with advanced renal disease, were increased in male rats. Renal tubular hyperplasia was seen in 2/55 high dose male rats, and renal tubular

adenomas were seen in 4/55 low dose and 8/55 high dose male rats; none were seen in the vehicle controls.

Mononuclear cell leukemia in female rats occurred with a dose-related trend and the incidences in the dosed groups were greater than in the vehicle controls (vehicle control, 9/55; low dose, 15/55; high dose, 22/55;  $p < 0.05$ ). The historical incidence of leukemia in water gavage vehicle control female F344/N rats is  $25 \pm 15$  percent and in untreated controls is  $19 \pm 7$  percent.

Compound-related lesions observed in the liver of male mice given 0, 50, and 100 mg/kg hydroquinone included anisokaryosis (0/55, 2/54, 12/55)<sup>1</sup>, syncytial alteration (5/55, 3/54, 25/55), and basophilic foci (2/55, 5/54, 11/55). The incidences of hepatocellular adenomas were increased in dosed male mice (9/55, 21/54, 20/55), but the increases were offset by decreases in the incidences of hepatocellular carcinomas (13/55, 11/54, 7/55). The incidences of hepatocellular neoplasms, primarily adenomas, were increased in dosed female mice (3/55, 16/55, 13/55).

Follicular cell hyperplasia of the thyroid gland was increased in dosed mice (male: 5/55, 15/53, 19/54; female: 13/55, 47/55, 45/55). Follicular cell adenomas were seen in male mice (2/55, 1/53, and 2/54) and female mice (3/55, 5/55, and 6/55). A follicular cell carcinoma was seen in a seventh high dose female mouse. The highest observed incidence of follicular cell adenomas or carcinomas (combined) in historical water gavage vehicle control female B6C3F1 mice is 3/48 (6 percent).

In conclusion, these studies showed "some evidence" of carcinogenic activity of hydroquinone as follows:

- Male F344/N rats: Marked increases in tubular cell adenomas of the kidney
- Female F344/N rats: Increases in mononuclear cell leukemia
- Female B6C3F1 mice: Increases in hepatocellular neoplasms, mainly adenomas
- Female and male B6C3F1 mice: Thyroid follicular cell hyperplasia
- Male B6C3F1 mice: Anisokaryosis, multinucleated hepatocytes, and basophilic foci of the liver.

NTP interprets the findings of each bioassay with regard to the strength of the experimental evidence. NTP defines "some evidence" of carcinogenicity as demonstrated by studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for

clear evidence. "Clear evidence" of carcinogenicity is considered demonstrated by studies that are interpreted as showing one of the following:

- A dose-related increase of malignant neoplasms
- An increase of a combination of malignant and benign neoplasms
- A marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

NTP's conclusion for these studies is that there was "some evidence" of carcinogenic activity in male and female rats and in female mice.

On February 11, 1992, the Nonprescription Drug Manufacturers Association (NDMA) requested to meet with FDA to discuss the safety of hydroquinone, specifics of the NTP study, and its research plans related to that study (Ref. 10). That meeting was held on May 20, 1992 (Ref. 11). NDMA presented a research program to further evaluate hydroquinone's carcinogenic potential based on the oral bioassay studies NTP performed. NDMA also discussed projected timelines for completing the proposed safety studies of hydroquinone. FDA also received additional data (Refs. 12 and 13) from NDMA, containing updates on chronic health effects testing for hydroquinone. These updates provided results of completed studies, including preliminary results for ongoing studies, and an outline of studies in the planning phase. FDA evaluated the studies and concluded that the available data are insufficient to rule out the potential carcinogenic risk from topically applied hydroquinone.

On July 10, 1996 (Ref. 14), FDA and NDMA met to discuss the safety of hydroquinone as an active ingredient in OTC skin bleaching drug products. Safety discussion points included the following:

- Mechanism of action of hydroquinone in tumor formation,
- Two year gavage study of hydroquinone in rats,
- Genotoxicity test results, and
- In vitro percutaneous absorption of hydroquinone through human skin.

FDA and NDMA agreed to present the data concerning the safety of hydroquinone with respect to an oral carcinogenicity study to FDA's CDER CAC. Subsequently, on December 4, 1996 (Ref. 15), information from the July 10, 1996, meeting and the 1989 NTP draft technical report were discussed at a CAC meeting. A majority of the CAC members agreed that the available data are insufficient to rule out the potential carcinogenic risk from topically applied

hydroquinone and recommended that additional studies be performed to assess the safety of skin bleaching drug products containing 2-percent hydroquinone. The CAC indicated that a dermal carcinogenicity study, conducted in an appropriate model with functioning melanocytes, must be performed on hydroquinone to assess both its topical and systemic tumorigenicity. In a December 7, 1998, letter (Ref. 16), FDA informed NDMA of our findings on its previous data submissions and the CAC recommendations. FDA also requested NDMA to provide an implementation schedule, which should include the timeframe for protocol development, protocol submission, study initiation and completion, and analysis of data. In an April 13, 1999, letter (Ref. 17), the Consumer Healthcare Products Association (CHPA; formerly NDMA) provided the following projected dates for additional safety studies of hydroquinone:

- May 1999—submit draft protocols for FDA review
  - August 1999—initiate 4-week range-finding study
  - November 1999—submit revised 2-year study protocol to FDA
  - January 2000—initiate the 2-year study
  - January 2002—conduct terminal sacrifice and necropsy
- Since April 13, 1999, CHPA has not provided any additional information.

#### *D. Occurrence of Exogenous Ochronosis*

Ochronosis refers to the deposition of polymerized homogentisic acid (HGA; 2,5-dihydroxyphenylacetic acid) as a grossly blue-black pigment in all collagen-containing structures. Ochronosis is classically associated with the autosomal recessively inherited metabolic disorder, alkaptonuria, in which the hepatic and renal enzyme HGA oxidase is absent (Refs. 18 and 19). Exogenous (acquired) ochronosis is a condition involving the deposition of blue-black pigment in the skin and is associated with the topical application of various chemicals. In severe cases, ochronosis may cause disfiguring and irreversible effects. FDA is aware that the occurrence of ochronosis has been reported following the topical application of hydroquinone.

Studies have shown that exogenous ochronosis caused by short- or long-term use of high or low concentrations of hydroquinone-containing bleaching creams has been well described in African blacks (Refs. 20 through 28). In 1975, Findlay, Morrison, and Simson (Ref. 20) first reported the development of exogenous ochronosis and pigmented

<sup>1</sup> Numbers reported for the vehicle control, low dose, and high dose groups, respectively.

colloid milium on the faces of black women in South Africa caused by prolonged use of skin bleaching creams containing hydroquinone (5 percent or greater). These lesions usually appeared after about 3 years of using the bleaching creams. The Panel reviewed this study and concluded that prolonged use of high concentrations (5 percent or more) of hydroquinone with exposure to sun may produce disfiguring effects (43 FR 51546 at 51549). Findlay and Beers (Ref. 21) found that up to 30 percent of outpatients in a dermatology clinic in South Africa wanted treatment of ochronosis following the use of skin lightening preparations containing hydroquinone for 3 years on average.

Phillips et al. (Ref. 22) reported 395 of 5,128 black patients who had used skin lightening products had ochronosis. The ochronosis was categorized as mild (darkening and thickening of the skin), moderate (large black bumps), or severe (larger intensively black caviar-like bumps).

According to Hardwick et al. (Ref. 23), in 1983 South Africa passed legislation that limited the concentration of hydroquinone in OTC skin lightening products to 2-percent in response to the severity of exogenous ochronosis in its black population. In addition, all skin lightening products had to contain a sunscreen with a minimum Sun Protection Factor of 5. In 1986, Hardwick et al. conducted a survey of adult South African blacks (both sexes) to investigate the relationship between exogenous ochronosis and the use of skin lightening products containing hydroquinone. Of 12 individuals who had begun using skin lightening products after 1983, seven (58 percent) had developed exogenous ochronosis.

Olumide, Odunowo, and Odiase (Ref. 24) discussed the common causes of facial hyperpigmentation in the black African population. One of the causes discussed was hydroquinone-induced exogenous ochronosis from bleaching creams containing hydroquinone. The physical signs included darkening and thickening of the skin, yellow-to-brown dome-shaped tiny bumps, and grayish-brown spots. Jordaan and Mulligan (Ref. 25) presented a case of a 39-year-old black South African woman with skin lesions on her face and neck. She had been using a skin bleaching cream containing an unknown concentration of hydroquinone for many years. Physical examination showed severe ochronosis on the cheeks, forehead, and neck. Weiss, de Fabbro, and Kolisang (Ref. 26) conducted a survey on black South African women, ages 16 to 40 years, to determine the prevalence of exogenous ochronosis caused by skin

lightening products containing hydroquinone. Of 65 women who had used skin lightening products after 1983, 42 (65 percent) had developed exogenous ochronosis.

Levin and Maibach (Ref. 27) presented some reasoning for the high prevalence of exogenous ochronosis among South African blacks. The high concentrations of hydroquinone used in South Africa skin-lightening products prior to 1984 were linked with increased incidence of exogenous ochronosis. Since the South African Government mandated a limit of 2-percent hydroquinone in skin bleaching creams in 1983, exogenous ochronosis still continues to occur and appears to be on the increase. Causes may be due to several factors in addition to hydroquinone. There was a marketed growth for use of an antiacne product containing resorcinol, also known as an ochronotic agent. Hydroquinone and resorcinol are often used together for a more rapid skin lightening agent. The predominant formulation for skin bleaching in South Africa includes hydroquinone and hydroalcoholic acid, which may contribute to the high incidence of exogenous ochronosis.

Mahe et al. (Ref. 28) conducted a questionnaire study on cosmetic use of bleaching creams on 368 dark-skinned women from sub-Saharan Africa who were patients at the dermatological center in Senegal. Also in a separate study, Mahe et al. recorded information on 425 women who actually used bleaching creams on a regular basis. Of the 368 women questioned, 194 (52.7 percent) were current users of bleaching products. Of the 425 users enrolled, 92-percent used products on the body. The active ingredients used included hydroquinone (89 percent of users), glucocorticoids (70 percent), mercury iodide (10 percent), caustic agents (17 percent), and products of unknown composition (13-percent). Complete skin examination of women using skin bleaching products revealed 14 cases of exogenous ochronosis.

Exogenous ochronosis was not extensively reported in the United States or the United Kingdom as a result of using OTC skin bleaching drug products containing 2-percent hydroquinone until after publication of the TFM for these drug products in 1982. In 1983, Cullison, Abele, and O'Quinn reported blue-black darkening of the face of a 50-year-old black woman (Ref. 18). This condition started on the right cheek and soon thereafter involved the entire face. For over 2 years, the woman had used a proprietary bleaching cream containing 2-percent hydroquinone to "brighten" her

complexion. When the darkening of the skin began to appear, the woman increased the application of the bleaching cream from twice a day to five or six times a day. Physical examination revealed a sooty blue-black darkening of the face without involvement of the eyes or ears. The darkening of the skin was relatively uniform, with some spots on the upper cheeks and the skin creases of the cheeks and forehead. A 2-millimeter (mm) biopsy specimen was taken and stained. The biopsy demonstrated a yellow-brown pigment present within mixed and swollen collagen bundles in the upper skin layer. These findings were interpreted as ochronosis.

Hoshaw, Zimmerman, and Menter (Ref. 29) described two black American women who had ochronosis-like pigmentation and colloid milium formation following the topical use of a 2-percent hydroquinone bleaching cream. The first black woman was a 75-year-old who had a 10-year history of pigmentation of the cheeks and nose in association with minimal itching. For the previous 2 years, she had used a 2-percent hydroquinone skin bleaching product to treat the pigmented areas. Physical examination disclosed multiple pigmented papules situated predominantly on the cheeks and extending around the lateral area of the eyes onto the forehead. There was an associated melasma-type macular pigmentation. The woman's condition was relatively unchanged 1 year later.

The second black woman was a 49-year-old who had a 2-year history of dark blotches on the face. During the previous 3-months, she had used a variety of 2-percent hydroquinone skin bleaching products to lighten her skin color. Instead of lightening, she noticed progressive darkening of the treated areas. Physical examination disclosed sharply separated areas of blue-black darkening of the skin over the cheeks, nose, and chin. The pigment was located essentially in discrete spots of less than 0.5 mm in size. In both cases, histological examination of a biopsy was consistent with ochronosis.

Tidman, Horton, and MacDonald (Ref. 30) reported a case of a 45-year-old Nigerian woman, resident in the United Kingdom for 7 years, who had a 7-month history of localized darkening of the face. This condition had been transiently preceded by erythema. Over a period of 10 years, the woman had intermittently applied to her face a proprietary depigmenting cream which contained 2-percent hydroquinone. Physical examination revealed a pronounced symmetrical darkening of the skin involving the cheek regions and, to a lesser extent, the nose and

chin. There was no evidence of spontaneous resolution after 11 months.

Conner and Braunstein (Ref. 31) reported a case of a 72-year-old black woman with a 1-month history of progressive darkening of her face. Since childhood, the woman had been applying a bleaching cream containing hydroquinone to her face in an attempt to lighten her complexion. Physical examination revealed blue-black spots along with patches on the forehead, cheek, and temporal regions. A biopsy specimen from the darkened skin led to a diagnosis of exogenous ochronosis.

Lawrence, et al. (Ref. 32) described two middle aged black women who reported unusual darkening of the face after using bleaching creams containing hydroquinone. One woman (62 years old) had applied a 1-percent hydroquinone bleaching cream for 2 to 3 years to the cheek area for mild darkening of the skin. The woman noted mild lightening of her skin during the first few months of use. After extended use, she noticed the return of the pigmentation, followed by diffuse darkening of the skin that was limited to the areas treated with the cream. Physical examination revealed dark spots across her cheeks.

The second woman (45 years old) had darkening of the skin on her face of 2 months' duration. The woman had used a 1-percent hydroquinone cream to lighten several post inflammatory lesions. After some initial lightening, she noted progressive darkening of the skin. Physical examination revealed a dark spot eruption extending over the bridge of her nose, the cheek, the eye areas, and across the forehead. The histopathologic findings of a biopsy specimen were consistent with ochronosis.

Howard and Furner (Ref. 33) presented a case of a 36-year-old Mexican-American woman with symptoms of darkening of the skin on her face after she used an OTC skin bleaching cream containing 2-percent hydroquinone for 4 months. Physical examination of the woman's face showed even blue-black, dark spots on her cheeks, chin, and forehead, as well as several dark spots on her gum line and inner cheek area. A biopsy specimen was consistent with exogenous ochronosis.

Diven, et al. (Ref. 34) reported a case of a 53-year-old black woman who noticed a progressive darkening of her face after applying a "skin whitener cream" and a cream containing 2-percent hydroquinone for a 2 to 3 month duration. Examination showed sooty blue-black spots and patches, which were prominent around the eye and

cheek areas. A biopsy specimen from the pigmented area showed the yellow-brown deposits in the skin characteristic of exogenous ochronosis.

Jordaan and Van Niekerk (Ref. 35) reported two cases of severe ochronosis with superimposed papular lesions after long-term application of skin lightening creams containing hydroquinone. The first case (a 56-year-old black man) had been using 6.5 to 7.5 percent hydroquinone periodically for many years. The second case (a 39-year-old black woman) had been using a skin lightening cream containing an unknown concentration of hydroquinone for 5 years. The woman had severe papular ochronosis on her face, forehead, and neck.

Martin, et al. (Ref. 36) reported two cases of exogenous ochronosis secondary to the topical use of hydroquinone containing bleaching creams. The first case (a 44-year-old woman) noticed progressive darkening of her skin for 3 years while using OTC bleaching creams. She had a grayish-black pigmentation localized to her cheeks, forehead, and the bridge of her nose, which corresponded to tiny grayish-black bumps. The second case (a 56-year-old black woman) had a history of facial pigmentation for 30 years while using many OTC skin bleaching creams. She had round dark spots localized to both temples and a purplish-black spot on the left lower eye area.

Snider and Thiers (Ref. 37) reported a case of exogenous ochronosis in a 59-year-old black woman who had a 5-year history of progressive darkening of the skin around her eyes. She had been using 2-percent hydroquinone skin bleaching cream once daily for many years. About 9 months before examination she had used 3-percent hydroquinone twice daily for 3 months, then 4-percent hydroquinone twice daily for 3 months, and then 4-percent hydroquinone with a sunscreen twice daily for 3 months. Examination showed numerous pinpoint blue-black spots around the eye area. A biopsy specimen revealed multiple scattered, elongated, curved, and oval deposits of ochronotic pigment within the collagen bundles.

Camarasa and Serra-Baldrich (Ref. 38) reported a case of a 45-year-old woman who had a 9-month history of darkening of the cheeks and eye area from using a skin lightening cream containing 2-percent hydroquinone. She was patch tested with a standard series, cosmetics, vehicles, and hydroquinone. The results showed this woman's reaction was consistent with the diagnosis of exogenous ochronosis.

Bowman and Leshner (Ref. 39) reported a 75-year-old black woman with

numerous discrete, 2- to 3-mm, firm, yellowish bumps on her forehead, cheeks, and chin; many had surrounding areas of dark spots. She was diagnosed with a case of primary multiple miliary osteoma cutis (MMOC), a rare disorder characterized by the appearance of numerous bony nodules on the face. She had used OTC topical acne medications and bleaching creams for 3 years in an attempt to treat the disorder. Several biopsies showed collections of homogenous yellow-brown pigment in the upper dermis, which also led to the diagnosis of exogenous ochronosis.

### III. FDA's Tentative Conclusions on Skin Bleaching Drug Products

A significant amount of research has been conducted on the skin bleaching ingredient hydroquinone, and a number of reports have appeared in the literature since publication of the TFM in 1982. As a result, FDA evaluated significant additional new data on the safety of hydroquinone. Although we cannot make a final determination on hydroquinone's potential to impair fertility, toxicology and carcinogenesis studies on orally administered hydroquinone conducted under the support of NTP (Refs. 1 and 2) have indicated "some evidence" of carcinogenicity in male and female rats and in female mice after gavage administration. "Some evidence" of carcinogenic activity is defined as studies that are interpreted as showing a chemically related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for "clear evidence" (e.g., same finding in two of the four sex/species groups, extensive malignancy, etc.). In these studies:

- Male rats had increased renal tubular cell adenomas without associated increases in nonneoplastic findings or bladder lesions;
- Female rats had increased mononuclear cell leukemia; and
- Female mice had increased hepatocellular neoplasms, mainly adenoma.

FDA's CDER CAC has evaluated the design, results, and NTP interpretation of these studies, and concurs with the NTP assessment. The CAC recommended additional studies, which have not been submitted to date. The evidence of carcinogenicity in animals in combination with the high absorption rate (57 percent) of hydroquinone demonstrated in humans does not allow FDA to rule out the potential carcinogenic risk from topically applied hydroquinone in humans. Further,

hydroquinone has been shown to cause disfiguring effects (ochronosis) after use of high concentrations (5 percent or greater) and at concentrations as low as 1 to 2-percent.

Skin bleaching products are drugs under section 201(g)(1)(C) of the act if they are intended to affect the structure or function of the body (e.g., products intended to suppress melanin pigment formation within skin cells). In evaluating the suitability of such drug products for OTC use, FDA considers, among other factors, the benefit-to-risk ratio of the drug. For OTC skin bleaching drug products, FDA tentatively concludes that there is no benefit to physical health that would justify the continued marketing of these products. Because the choice to use a drug is not considered an inadvertent exposure, risks may be outweighed by benefits, where they exist. Where the benefit appears low and use of the drug is proposed for an otherwise healthy target population, the risks should be minimal. For these OTC drug products, the sole intended benefit would be to improve the user's appearance by bleaching the skin.

The actual risk to humans from the use of hydroquinone has yet to be fully determined. There is, however, evidence of carcinogenicity related to hydroquinone in animals and disfiguring effects (ochronosis) in humans. Under these circumstances, the use of hydroquinone as an active ingredient in OTC skin bleaching drug products cannot be justified. Therefore, in light of the new data discussed in this document, FDA has reassessed the position stated in the 1982 TFM (47 FR 39108).

FDA now proposes that skin bleaching drug products should not be available OTC. FDA finds that because of the carcinogenic and ochronotic potential of hydroquinone, its use in skin bleaching drug products should be restricted to prescription use only, and users of such products should be closely monitored under medical supervision. FDA now tentatively concludes that skin bleaching drug products, including but not limited to those that contain hydroquinone, which have been reviewed by the Panel and FDA should be considered not GRASE. Accordingly, the proposed monograph (TFM) published in the **Federal Register** of September 3, 1982, which proposed 21 CFR part 358, subpart A (Skin Bleaching Drug Products for Over-The-Counter Human Use), is hereby withdrawn.

FDA emphasizes that this withdrawal does not in any way denigrate the scientific content of the Panel's report on these products or negate the

excellent work of the Panel in its long efforts to produce it. FDA recognizes that OTC skin bleaching drug products constitute a very small segment of the marketplace and that withdrawal of the proposed monograph does not affect FDA's authority to take action against OTC skin bleaching drug products that are unsafe and misbranded.

The only other skin bleaching active ingredient evaluated in this rulemaking was ammoniated mercury, which FDA declared to be not GRASE in the **Federal Register** of November 7, 1990 (55 FR 46914 at 46919). FDA now proposes that all skin bleaching drug products be considered new drugs within the meaning of section 201(p) of the act (21 U.S.C. 321(p)), for which approved NDAs under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314) are required for marketing. In the absence of an approved NDA, such a product would also be misbranded under section 502 of the act (21 U.S.C. 352). This proposal applies only to drugs marketed OTC, and it would amend § 310.545, which applies only to OTC drugs. However, FDA emphasizes that it regards all skin bleaching drug products, whether marketed on a prescription or OTC basis, to be new drugs. This does not preclude other OTC drugs from being considered for the OTC drug monograph on skin bleaching drug products (e.g., under the procedures in 21 CFR 330.14).

#### IV. Analysis of Impacts

FDA has examined the impacts of this proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). 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 may have a significant economic 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 of 1995 requires that agencies prepare a written statement and economic analysis before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the

private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year."

FDA concludes that this proposed rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The proposed rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current threshold after adjustment for inflation is \$115 million, using the most current (2003) Implicit Price Deflator for the Gross Domestic Product.

The purpose of this proposed rule is to establish that OTC skin bleaching drug products are not GRASE and are misbranded. Most skin bleaching drug products that contain hydroquinone as an active ingredient are currently marketed as OTC drug products. Some such products (usually those containing above 2-percent hydroquinone) are marketed by prescription. FDA's Drug Listing System identifies approximately 200 products containing hydroquinone in strengths from 0.4 to 5.0 percent (Table 1).

TABLE 1.—NUMBER OF SKIN BLEACHING DRUG PRODUCTS CONTAINING VARIOUS CONCENTRATIONS OF THE ACTIVE INGREDIENT HYDROQUINONE

Percent Hydroquinone	Number of Products
5	2
4	65
3	8
2	110
<2	21

About two-thirds of these products appear to be marketed as OTC drugs. These products are marketed by approximately 65 different manufacturers, most of which are considered to be small entities, using the U.S. Small Business Administration designations for this industry (750 employees). FDA believes that any other unidentified manufacturer of these products is also likely to be a small entity.

FDA tentatively concludes that the benefits of OTC skin bleaching drug products are insignificant when compared to the potential risks and that this proposed rule would benefit society because it would eliminate a potentially unsafe drug product. The proposed rule would prohibit the continued marketing of hydroquinone as an OTC drug product and require a NDA under 21 CFR part 314 for marketing.

FDA acknowledges that this proposed rule would have an impact on consumers who use OTC skin bleaching drug products containing hydroquinone to lighten limited areas of hyperpigmented skin. They will no longer be able to purchase these OTC drug products after current inventories are depleted.

The benefit of removing OTC skin bleaching drug products from the market will be a reduction in the number of cases of ochronosis that would otherwise occur each year. However, FDA has limited information to assign a monetary value to the prevention and treatment of ochronosis and the direct medical costs and indirect costs, such as psychological suffering, resulting from disfigurement due to ochronosis.

The 65 manufacturers of these products will incur the majority of the costs of this proposed rule, in the form of lost sales. They would also incur the costs of obtaining an approved NDA if they wished to continue to market their product(s) by prescription. Manufacturers who have followed the FDA-NDMA (CHPA) dialogue on these hydroquinone drug products should have known for some time that if additional adequate data were not provided to support safety, a nonmonograph status for these products would occur. Thus, this economic analysis, together with other relevant sections of this document, serves as FDA's initial regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

#### V. Paperwork Reduction Act of 1995

This proposed 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.

#### VI. Environmental Impact

FDA 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.

#### VII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule, if finalized as proposed, would have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to "construe \* \* \* a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Section 751 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that " \* \* \* no State or political subdivision of a State may establish or continue in effect any requirement-- \* \* \* that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 et seq.)."

Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See Section 751(b) through (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.) This proposed rule, if finalized as proposed, would establish that OTC skin bleaching drug products are not GRASE and are misbranded. Although any final rule would have a preemptive effect, in that it would preclude States from promulgating requirements related to OTC skin bleaching drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied preemption may arise. See *Geier v. American Honda Co.*, 529 US 861 (2000).

FDA believes that the preemptive effect of the proposed rule, if finalized as proposed, would be consistent with Executive Order 13132. Section 4(e) of the Executive order provides that "when

an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings." FDA is providing an opportunity for State and local officials to comment on this rulemaking.

#### VIII. Request for Comments

Interested persons may submit to the Division of Dockets Management (see **ADDRESSES**) written or electronic comments regarding this document and on FDA's economic impact determination. Submit a single copy of electronic comments or two paper copies of any mailed comments, except that individuals may submit one paper copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management (see **ADDRESSES**) between 9 a.m. and 4 p.m., Monday through Friday.

#### IX. Proposed Effective Date

Because there will be no need to reformulate or relabel any of these products, FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register**.

#### X. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) under Docket No. 1978N-0065 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

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7. Bio/dynamics Inc., "A Two-Generation Reproduction Study in Rats With Hydroquinone," Project No. 87-3219, 1989, in OTC Vol. 16ATFM2.

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9. Bucks, D. A. W. et al., "Percutaneous Absorption of Hydroquinone in Humans: Effect of 1-Dodecylazacycloheptan-2-One (Azone) and the 2-Ethylhexyl Ester of 4-(Dimethylamino)Benzoic Acid (Escalol 507)," *Journal of Toxicology and Environmental Health*, 24:279-288, 1988.

10. Comment No. LET2.

11. Comment No. MM1.

12. Comment No. RPT3.

13. Comment No. RPT5.

14. Comment No. MM2.

15. Comment No. MM3.

16. Comment No. LET16.

17. Comment No. C24.

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25. Jordaan, H. F. and R. P. Mulligan, "Actinic Granuloma-Like Change in Exogenous Ochronosis: Case Report," *Journal of Cutaneous Pathology*, 17:236-240, 1990.

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#### 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, the proposed rule that published on September 3, 1982 (47 FR 39108), is withdrawn and it is proposed that 21 CFR part 310 be 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 revising paragraphs (a)(17), (d) introductory text, and (d)(1) and by adding new paragraph (d)(41) to read as follows:

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

(a) \* \* \*

(17) *Skin bleaching drug products*—(i) *Ingredient—Approved as of May 7, 1991.*

Mercury ammoniated

(ii) *Ingredients—Approved as of [date 30 days after date of publication in the Federal Register].*

Hydroquinone

Any other ingredient

\* \* \* \* \*

(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 into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(41) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(2)(i), (a)(3)(i), (a)(4)(i), (a)(6)(i)(A), (a)(6)(ii)(A), (a)(7) (except as covered by paragraph (d)(3) of this section), (a)(8)(i), (a)(10)(i) through (a)(10)(iii), (a)(12)(i) through (a)(12)(iv)(A), (a)(14) through (a)(15)(i), (a)(16), (a)(17)(i), and (a)(18)(i)(A) of this section.

\* \* \* \* \*

(41) [30 days after date of publication in the **Federal Register**], for products subject to paragraph (a)(17)(ii) of this section.

Dated: August 7, 2006.

**Jeffrey Shuren,**

*Assistant Commissioner for Policy.*

[FR Doc. E6-14263 Filed 8-28-06; 8:45 am]

BILLING CODE 4160-01-S

## DEPARTMENT OF THE TREASURY

### Internal Revenue Service

#### 26 CFR Part 1

[REG-121509-00]

RIN 1545-AY54

#### **Exclusion From Gross Income of Previously Taxed Earnings and Profits, and Adjustments to Basis of Stock in Controlled Foreign Corporations and of Other Property**

**AGENCY:** Internal Revenue Service (IRS), Treasury.

**ACTION:** Notice of proposed rulemaking.

**SUMMARY:** This document contains proposed regulations that provide guidance relating to the exclusion from gross income of previously taxed earnings and profits under section 959 of the Internal Revenue Code (Code) and related basis adjustments under section 961 of the Code. These regulations reflect relevant statutory changes made in years subsequent to 1983. These regulations also address a number of issues that the current section 959 and section 961 regulations do not clearly answer. These regulations, in general, will affect United States shareholders of controlled foreign corporations and their successors in interest.

**DATES:** Written or electronic comments and requests for a public hearing must be received by November 27, 2006.

**ADDRESSES:** Send submissions to: CC:PA:LPD:PR (REG-121509-00), Internal Revenue Service, P.O. Box 7604, Ben Franklin Station, Washington, DC 20044 or send electronically, via the IRS Internet site at <http://www.irs.gov/regs> or via the Federal eRulemaking Portal at <http://www.regulations.gov> (IRS REG-121509-00).

**FOR FURTHER INFORMATION CONTACT:** Concerning the proposed regulations, Ethan Atticks, (202) 622-3840; concerning submissions of comments, Kelly Banks, (202) 622-0392 (not toll-free numbers).

#### **SUPPLEMENTARY INFORMATION:**

##### **Background**

This document contains proposed amendments to 26 CFR part 1 under sections 959 and 961. Section 959(a)(1) generally provides an exclusion from

the gross income of a United States shareholder for distributions of earnings and profits of a foreign corporation attributable to amounts which are, or have been, included in a United States shareholder's gross income under section 951(a). Section 959(a)(2) excludes from the gross income of a United States shareholder earnings and profits attributable to amounts which are, or have been, included in the gross income of a United States shareholder under section 951(a) which would, but for section 959(a)(2), be again included in gross income of a United States shareholder under section 951(a)(1)(B) as an amount determined under section 956 (section 956 amounts). Earnings and profits of a foreign corporation included in a United States shareholder's gross income under section 951(a) are referred to as previously taxed earnings and profits or previously taxed income (PTI).

Section 959(b) generally provides that for purposes of section 951(a), PTI shall not, when distributed through a chain of ownership described in section 958(a), be included in the gross income of a controlled foreign corporation (CFC) in such chain for purposes of the application of section 951(a) to such CFC.

Section 959(c) generally provides for the allocation of distributions by a foreign corporation to three different categories of the corporation's earnings and profits: (1) PTI attributable to section 956 amounts that are included in the gross income of a United States shareholder under section 951(a)(1)(B) and section 956 amounts that would have been so included but for section 959(a)(2), (2) PTI attributable to amounts included in gross income under section 951(a)(1)(A), and (3) other earnings and profits (non-PTI). Section 959(f) provides for the allocation of section 956 amounts first to PTI arising from a United States shareholder's income inclusions under section 951(a)(1)(A) and then to non-PTI. In addition, section 959(f) provides a priority rule under which actual distributions of earnings and profits are taken into account before section 956 amounts.

Certain amounts are treated as amounts included in the gross income of a United States shareholder under section 951(a)(1)(A) for purposes of section 959. For example, section 959(e) generally provides that any amount included in the gross income of any person as a dividend by reason of subsection (a) or (f) of section 1248 is treated for purposes of section 959 as an amount included in the gross income of such person under section 951(a)(1)(A).

Section 961 authorizes the Secretary of the Treasury to promulgate

regulations adjusting the basis of stock in a foreign corporation, as well as the basis of other property by reason of which a United States person is considered under section 958(a) to own stock in a foreign corporation. Section 961(a) generally provides for an increase in a United States shareholder's basis in its CFC stock, or in the property by reason of which it is considered to own such stock, by the amount required to be included in its gross income under section 951(a) with respect to such stock.

Under section 961(b), and the regulations thereunder, when a United States person receives an amount which is excluded from gross income under section 959(a), the adjusted basis of the foreign corporation stock or the property by reason of which the shareholder is considered to own such stock is reduced by the amount of the exclusion. In addition, section 961(c) generally provides for regulations under which adjustments similar to those provided for under section 961(a) and (b) are made to the basis of stock in a CFC which is owned by another CFC (and certain other CFCs in the chain) for the purpose of determining the amount included under section 951 in the gross income of a United States shareholder.

Section 959 was enacted so that PTI is excluded from gross income and, thus, not taxed again when distributed by the foreign corporation. Moreover, section 959 effects the relevant gross income exclusion at the earliest possible point. Thus, the "allocation of distribution" rules of section 959(c) ensure that distributions from the foreign corporation are to be paid first out of earnings and profits attributable to amounts that have been previously included in income by the United States shareholders. Accordingly, as a result of its section 951(a)(1) inclusion, a United States shareholder is made whole by receiving, without further U.S. tax, PTI attributable to its stock in a foreign corporation before it receives any taxable distributions from the foreign corporation. Section 961, which adjusts basis in the stock in a foreign corporation for PTI attributable to such stock, also ensures that PTI is not taxed twice if the stock in the foreign corporation is sold before the PTI is distributed.

The existing regulations under sections 959 and 961 were published in 1965. See TD 6795 (1965-1 CB 287). Minor amendments were made to the regulations in 1974, 1978, and 1983. See TD 7334 (1975-1 CB 246); TD 7545 (1978-1 CB 245); TD 7893 (1983-1 CB 132). The regulations have not been updated since 1983 to reflect relevant