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**Termination of Provisional Listings of FD&C Red No. 3 for Use in..., 55 FR 3516-01**

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55 FR 3516-01, 1990 WL 352835(F.R.)  
RULES and REGULATIONS  
DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Food and Drug Administration  
21 CFR Parts 81 and 82  
[Docket Nos. 76C-0044 and 76N-0366]

Termination of Provisional Listings of FD&C Red No. 3 for Use in Cosmetics and Externally Applied Drugs and of Lakes of FD&C Red No. 3 for All Uses

Thursday, February 1, 1990

AGENCY: Food and Drug Administration.

ACTION: Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing the expiration of the provisional listing for FD&C Red No. 3 for use in coloring cosmetics and externally applied drugs and for all uses of the lakes of FD&C Red No. 3. FDA is not extending the provisional listing of these uses of FD&C Red No. 3 and its lakes because the agency has concluded, on the basis of animal experiments that were performed as a condition of these provisional listings, that the color additive and its lakes have not been shown to be safe. In particular, the color additive causes a carcinogenic response in rats. Therefore, FD&C Red No. 3 may not be added to cosmetics and externally applied drugs, and the lakes of FD&C Red No. 3 may not be added to food, drugs, or cosmetics. Published elsewhere in this issue of the Federal Register is a notice denying the color additive petition for the permanent listing of FD&C Red No. 3 for use in cosmetics and externally applied drugs.

**EFFECTIVE DATE:** January 29, 1990.

**FOR FURTHER INFORMATION CONTACT:** Catherine J. Bailey, Center for Food Safety and Applied Nutrition (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

**SUPPLEMENTARY INFORMATION:** FDA is announcing the termination of the provisional listing of FD&C Red No. 3 for use in cosmetics and externally applied drugs and of the provisional listing of the lakes of FD&C Red No. 3 for all uses. Published elsewhere in this issue of the Federal Register is a notice denying the color additive petition for the permanent listing of FD&C Red No. 3 for use in cosmetics and externally applied drugs (the denial notice).

### **I. Background and Procedural History**

FD&C Red No. 3, a bluish red color of the xanthene class, is currently identified in Chemical Abstracts as the disodium salt of 3', 6'-dihydroxy-2', 4', 5', 7'-tetraiodospiro[isobenzofuran-1(3H), 9'-[9H]xanthen]-3-one, (CAS Reg. No. 16423-68-0). FDA and industry communications have established the common name "fluorescein" as a means of identifying derivatives of that chemical moiety. Therefore, FDA identifies this color additive as principally the disodium salt of 2', 4', 5', 7'-tetraiodofluorescein (CAS Reg. No. 16423-68-0) with smaller amounts of the disodium salts of 2', 4', 5'-triiodofluorescein (CAS Reg. No. 56254-06-9) and 2', 4', 7'-triiodofluorescein (CAS Reg. No. 83498-90-2). The designation "FD&C Red No. 3" is permitted only for those batches of the color additive that the agency has certified to be in compliance with § 74.303 (21 CFR 74.303). Uncertified material is commonly called erythrosine or other names, including Colour Index (C.I.) Acid Red 51; C.I. No. 45430; and C.I. Food Red 14.

The Color Additive Amendments of 1960 (Title II, Pub. L. 86-618, 74 Stat. 404-407) (the amendments) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321 et seq., require premarket clearance of any color additive that is represented for use in or on food, drugs, cosmetics, certain medical devices, or the human body.

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Under the amendments, a color additive may be approved only if data establish that it is safe under its intended conditions of use. Recognizing that many color additives, including lakes of color additives, were already in use at the time of the amendments, Congress provided, under section 203(b) of the transitional provisions of the amendments, for the provisional listing of these substances while they were being tested for safety. Because FD&C Red No. 3 and its lakes were in use at the time the amendments were enacted, they were provisionally listed for all food, drug, and cosmetic uses in the Federal Register of October 12, 1960 (25 FR 9759).

Thereafter, a color additive petition (CAP 8C0067) for the permanent listing of FD&C Red No. 3 for use in food, including dietary supplements, and ingested drugs was submitted by the Certified Color Industry Committee (now the Certified Color Manufacturers' Association (CCMA)). A notice of filing of the petition was published in the Federal Register of July 2, 1968 (33 FR 9627). In the Federal Register of May 8, 1969 (34 FR 7446), FD&C Red No. 3 was listed pursuant to 21 U.S.C. 376 for use in food and ingested drugs under §§ 8.242 and 8.4102 (21 CFR 8.242 and 8.4102). These regulations were subsequently recodified at 21 CFR 74.303 and 74.1303.

In 1973, the Toilet Goods Association, Inc., (now the Cosmetic, Toiletry, and Fragrance Association, Inc., (CTFA), 1110 Vermont Ave. NW., Washington, DC 20005) submitted a petition (CAP 9C0096) for the use of FD&C Red No. 3 for coloring externally applied drugs and cosmetics, including lipsticks. The filing of this petition was announced in the Federal Register of August 6, 1973 (38 FR 21199). Subsequently, in a letter dated May 14, 1974, CTFA requested that its petition be amended to include listing FD&C Red No. 3 in cosmetics for eye-area use. FDA published an amended filing notice for the petition in the Federal Register of March 5, 1976 (41 FR 9584), to include the listing of FD&C Red No. 3 for eye-area use and all types of cosmetics that are subject to ingestion. However, because the petitioner has not responded to FDA's request of May 14, 1976, for information related to eye-area use of the color additive, FDA considers the portion of the petition relating to listing of FD&C Red No. 3 for eye-area use to be withdrawn without prejudice in accordance with the provisions of 21 CFR 71.6(c).

Although it is not the petitioner for the permanent listing of the cosmetic and externally applied drug uses, CCMA has submitted much of the data concerning the safety of FD&C Red No. 3 because of the organization's overall interest in the status of the color additive. Thus, CCMA and CTFA will hereafter be referred to collectively as the proponents of FD&C Red No. 3.

Because there were questions concerning general regulations for lakes of color additives, the lakes of FD&C Red No. 3 were not permanently listed and, instead, have continued to be provisionally listed for use as a coloring agent in food, drugs, and cosmetics. Food uses of the lakes include nuts, chewing gum, baked goods, and soft candy. Ingested drug uses include tablet formulations and liquid preparations; cosmetic uses include creams and lotions; face and body powder; and dry, liquid, and cream rouges.

FD&C Red No. 3 lakes have two separate provisional listings. First, FD&C Red No. 3 lakes are provisionally listed for food, drug, and cosmetic use under § 81.1(a) (21 CFR 81.1(a)); the specifications for certification of these lakes of FD&C Red No. 3 are set out in § 82.51 (21 CFR 82.51). Under § 82.51, FD&C Red No. 3 lakes may be prepared using only FDA certified batches of the color additive, alumina, and the cations of aluminum and/or calcium. FD&C Red No. 3 lakes must then be batch certified by FDA.

\*3517 Second, there are lakes of FD&C Red No. 3 that are limited to drug and cosmetic use; they are referred to as D&C Red No. 3 lakes. D&C Red No. 3 lakes are provisionally listed under § 81.1(b) (21 CFR 81.1(b)); the specifications for certification of these lakes are set out in § 82.1051 (21 CFR 82.1051). Under § 82.1051, D&C Red No. 3 lakes may be prepared using uncertified batches of the color additive, substrata, and cations as provided for under paragraph § 82.1051(a)(1). Section 82.1051(b) requires that the final material be batch certified by FDA as a D&C Red No. 3 lake.

The use of FD&C Red No. 3 in cosmetics and externally applied drugs, as well as all uses of the lakes of the color additive, have remained provisionally listed under § 81.1. FDA established a closing date of October 2, 1983, for the provisionally

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listed uses of FD&C Red No. 3 in the Federal Register of March 27, 1981 (46 FR 18954). At that time, the agency conditioned the extension of the provisional listing of the color additive upon the submission by October 2, 1982, of final reports of new chronic toxicity studies. The agency had required that new chronic toxicity studies be done because studies previously submitted were not adequate under then current standards to establish the safety of the color additive for ingested uses.

The October 2, 1983, closing date for the provisionally listed uses of FD&C Red No. 3 was further postponed by FDA in a series of final rules published in the Federal Register. A detailed description of the procedural history of the provisionally listed uses of FD&C Red No. 3 is set forth in the denial notice published elsewhere in this issue of the Federal Register. The current closing date of January 29, 1990, was established by FDA by final rule published in the Federal Register of October 30, 1989 (54 FR 43961).

Despite these numerous extensions of the closing date for the provisionally listed uses of FD&C Red No. 3, the proponents have not, as shown below and as discussed in detail in the denial notice, established that the color additive is safe, to a reasonable certainty, for the petitioned uses.

## II. Toxicity Studies of FD&C Red No. 3

The continued provisional listing of FD&C Red No. 3 was conditioned upon, among other requirements, the submission to FDA by October 2, 1982, of final reports of chronic toxicity studies in rats and in mice (21 CFR 81.27(d)). In response to this requirement, the proponents of FD&C Red No. 3 sponsored two chronic feeding studies. In these studies, FD&C Red No. 3 was administered in the diet to Sprague-Dawley Charles River Albino CD rats and in the diet to Charles River CD-1 mice. The final reports of these chronic feeding studies were submitted to FDA in May and October 1982. In addition to the chronic feeding studies, the proponents of FD&C Red No. 3 have submitted other data and information concerning the toxicity of the color additive. All of the studies, data, and other information submitted by the proponents is described in detail in the denial notice published elsewhere in this issue of the Federal Register; that description is incorporated herein.

FDA has reviewed the final reports of the chronic feeding studies as well as all other available toxicological information on FD&C Red No. 3. Based upon the results of the chronic toxicity studies, FDA has concluded that FD&C Red No. 3 is an animal carcinogen. In particular, in the chronic feeding study in rats, exposure to the color additive was associated with an increased incidence of combined thyroid follicular cell adenomas and carcinomas in male rats fed at the highest level (4.0 percent). FDA's evaluation of the long-term feeding studies of FD&C Red No. 3 is discussed in detail in the denial notice published elsewhere in this issue of the Federal Register; that discussion is incorporated herein. Thus, FDA has determined that FD&C Red No. 3 is an animal carcinogen.

The proponents of FD&C Red No. 3 have hypothesized that the thyroid tumors in male rats in the chronic study were the result of a secondary mechanism of action and, thus, were not caused by FD&C Red No. 3. In particular, the proponents assert that the available evidence demonstrates that FD&C Red No. 3 itself, or iodine released by the color additive, causes a thyroid hormone imbalance; that imbalance then leads to an increased incidence of tumors.

In such circumstances, the proponents argue, there is a threshold level for the effects that lead to this hormonal imbalance, and that below this threshold, the ingestion of FD&C Red No. 3 will not affect thyroid hormone levels and tumors will not be induced. Accordingly, the proponents claim that the data demonstrating a threshold level of effects will permit FDA to establish safe conditions of use for FD&C Red No. 3.

In an effort to establish the secondary mechanism hypothesis as well as to establish a threshold for this effect, the proponents have sponsored two 60-day studies in rats; the results of these studies were submitted to the agency in January 1989 and August 1989. The proponents also submitted an absorption, distribution, and metabolism study of FD&C Red No. 3 in rats in February 1989. These studies, as well as other data and information submitted by the proponents to support their secondary mechanism hypothesis, are described in detail in the denial notice published elsewhere in this issue of the Federal Register; that description is incorporated herein.

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The agency has reviewed the reports of all relevant studies as well as all other toxicological information that bears on the hypothesis of a secondary mechanism, and has concluded that the data do not establish that the carcinogenic effect of FD&C Red No. 3 is due to a secondary mechanism. The denial notice published elsewhere in this issue of the Federal Register discusses at length FDA's evaluation of and conclusions based upon the data submitted to support the proponents' hypothesis that FD&C Red No. 3 operates as a secondary oncogen; that discussion is incorporated herein.

The final toxicity study reports, the agency's evaluations of these studies, and all other information relied upon by the agency in reaching its decision are on file at the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, under Docket No. 76C-0044, and may be reviewed between 9 a.m. and 4 p.m., Monday through Friday.

### III. Termination of the Provisional Listings

Although section 203(a) of the transitional provisions of the amendments provides for the provisional listing of a color additive "pending the completion of the scientific investigations needed as a basis for making determinations as to listing of such additives," section 203(a)(2) authorizes the Secretary to terminate the postponement of the closing date "at any time if he finds \* \* \* that by reason of a change in circumstances the basis for such postponement no longer exists \* \* \*." In addition, section 203(d)(1)(E) provides "for the termination of a provisional listing \* \* \* of a color additive or particular use thereof forthwith whenever in [the Secretary's] judgment such action is necessary to protect the public health."

In the case of the provisionally listed uses of FD&C Red No. 3, FDA finds that both a change in circumstances and protection of the public health require that the provisional listings for use of \*3518 FD&C Red No. 3 and for the lakes of FD&C Red No. 3 be terminated. As discussed above, the agency has completed its review of the data submitted in support of the petition for the permanent listing of FD&C Red No. 3 for use in cosmetics and in externally applied drugs and has concluded that the available evidence does not establish the safety of the color additive. Thus, the proponents of FD&C Red No. 3 have not sustained their burden under the act. Accordingly, the agency is denying the pending petition. Accordingly, pursuant to the transitional provisions of the amendments, there is no basis on which to continue the provisional listings for these uses.

In addition, as set forth above, the agency has determined, based upon tests that were appropriate for evaluating the safety of the uses of this color additive and its lakes, that FD&C Red No. 3 is an animal carcinogen. Although the proponents of FD&C Red No. 3 have hypothesized that the oncogenic effect of FD&C Red No. 3 is the result of a secondary mechanism, the data submitted by the proponents do not establish this hypothesis. Accordingly, FD&C Red No. 3 is deemed unsafe (21 U.S.C. 376(b)(1)(5)(B)). In such circumstances, FDA concludes that extension of the provisionally listed uses of the color additive in cosmetics and externally applied drugs is not consistent with the protection of the public health. The agency has likewise concluded that extension of the provisional listing for the lakes of FD&C Red No. 3 is not warranted because the toxicity data for the color additive must necessarily be imputed to lakes that use the color additive. In addition, there are no separate safety data that independently establish the safety of the lakes of FD&C Red No. 3. For these reasons, the agency has also concluded that extension of the provisional listing of the lakes of FD&C Red No. 3 is not appropriate.

Based upon the foregoing, FDA has decided not to issue a further extension of the provisional listings of this color additive for use in cosmetics and externally applied drugs and of the lakes of this color additive for use in food, drug, and cosmetics. As a result of the agency's decisions, all provisional listings of FD&C Red No. 3 terminate on January 29, 1990.

Accordingly, under the transitional provisions of the Color Additive Amendments of 1960, FDA announces that: (1) The provisional listings of FD&C Red No. 3 for use in cosmetics and externally applied drugs and of the lakes of FD&C Red No. 3 in food, drug, and cosmetic products have expired; (2) all certificates heretofore issued for batches of FD&C Red No. 3 and all mixtures containing this color additive for use in cosmetics and externally applied drugs and all certificates issued for batches of FD&C Red No. 3 lakes and D&C Red No. 3 lakes are cancelled as of January 29, 1990; and (3) after January 29, 1990, the addition of FD&C Red No. 3 to cosmetics and externally applied drugs or the addition of the lakes of FD&C Red No. 3 to food, drug, or cosmetic products will cause such products to be adulterated within the meaning of sections 402, 501,

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and 601 of the act (21 U.S.C. 342, 351, and 361) and to be subject to regulatory action.

FDA has considered whether any health concern regarding the use of this color additive or its lakes represents an acute, imminent hazard, and has concluded that it does not. Therefore, because the risks posed by FD&C Red No. 3 result from chronic, long-term exposure, the protection of the public health does not require the recall from the market or the destruction of any food, drug, or cosmetic preparations to which the provisionally listed color additive or its lakes has already been added.

Manufacturers of new drugs and new animal drugs that contain FD&C Red No. 3 or its lakes and that are subject to the prohibition set forth below may either discontinue use of the color additive or its lakes or substitute different color additives in accordance with the provisions of 21 CFR 314.70(b)(2)(i) and (d)(4) or 21 CFR 514.8(d)(3) and (e), as appropriate. If a substitute color additive is not used, the human drug manufacturer shall describe the change fully in the next annual report as required under 21 CFR 314.81(b)(2)(iv)(b). If a substitute color additive is used, the manufacturer shall file with FDA a supplemental new drug application or a supplemental new animal drug application containing data describing the new composition and showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug, or that the assay and control procedures have been revised to make them adequate.

The applicant shall also submit data to establish the stability of the revised formulation. If the available data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, the applicant shall submit a commitment to test the stability of marketed batches at reasonable intervals, to submit to FDA those data as they become available, and to recall from the market any batch found to fall outside the approved specifications for the drug.

Each sponsor of a notice of claimed investigational exemption for a new drug (IND) or a notice of claimed investigational exemption for a new animal drug (INAD) containing FD&C Red No. 3 or a lake of FD&C Red No. 3 and that is subject to the prohibition set forth for the order below should promptly amend the IND and INAD to indicate that the color additive has been deleted or a different color additive has been substituted.

FDA is aware that supplies of alternative color additives and labeling may be difficult to obtain immediately. Consequently, food, drug, and cosmetic labeling that states that the product contains "artificial color" or that specifically identifies FD&C Red No. 3 or its lakes (including D&C Red. No. 3 lakes) may continue to be used with the uncolored product or with products containing alternative colors during the time necessary to obtain supplies of revised labeling or until January 29, 1991, whichever comes first.

By making appropriate revisions in 21 CFR parts 81 and 82, the order set forth below effectuates the announcement that FDA has terminated the provisional listings of FD&C Red. No. 3 for certain uses and its lakes for all uses.

The agency has analyzed the economic effects of this action and has determined that it does not meet the criteria for a major rule in Executive Order 12291. Further, although this action is exempt from the Regulatory Flexibility Act because it was not preceded by a proposed rule, FDA has considered the effect of this action on small entities, including small businesses, and has determined that no significant adverse effect will derive from this action. A copy of the agency's economic assessment is on file with the Dockets Management Branch (address above) under Docket No. 76C-0044.

The agency has carefully considered the potential environmental effects of this action. FDA has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement is not required. The agency's finding of no significant impact and the evidence supporting that finding, contained in an environmental assessment, is on file with the Dockets Management Branch (address above) under Docket No. 76C-0044 and may be seen between 9 a.m. and 4 p.m., Monday through Friday.

Notice and public procedure are not necessary prerequisites to promulgating \*3519 these regulations because section 203(d)(2) of Pub. L. 86-618 so provides.

## List of Subjects

### **21 CFR Part 81**

Color additives, Color additives provisional list, Cosmetics, Drugs.

### **21 CFR Part 82**

Color additives, Color additive lakes, Color additives provisional list, Cosmetics, Drugs.

Therefore, under section 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 376), and under the transitional provisions of the Color Additive Amendments of 1960 (74 Stat. 404-407 (21 U.S.C. 376, note)), and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), 21 CFR parts 81 and 82 are amended as follows:

## **PART 81—GENERAL SPECIFICATIONS AND GENERAL RESTRICTIONS FOR PROVISIONAL COLOR ADDITIVES FOR USE IN FOODS, DRUGS, AND COSMETICS**

1. The authority citation for 21 CFR part 81 continues to read as follows:

Authority: Secs. 701, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371, 376, 376 note).

### **§ 81.1 [Amended]**

2. Section 81.1 Provisional lists of color additives is amended in the table of paragraph (a) by removing the entry for “FD&C Red No. 3”.

3. Section 81.10 is amended by adding new paragraph (u) to read as follows:

### **§ 81.10 Termination of provisional listings of color additives.**

\* \* \* \* \*

(u) FD&C Red No. 3. Having concluded that FD&C Red No. 3 causes cancer in rats, the agency hereby terminates the provisional listing of FD&C Red No. 3 for use in cosmetics and externally applied drugs and the provisional listing of the lakes of FD&C Red No. 3 for use in food, drug, and cosmetic products, effective January 29, 1990.

### **§ 81.27 [Removed]**

4. Section 81.27 Conditions of provisional listing is removed.

5. Section 81.30 is amended by adding new paragraph (u) to read as follows:

### **§ 81.30 Cancellation of certificates.**

\* \* \* \* \*

(u)(1) Certificates issued for FD&C Red No. 3 and all mixtures containing this color additive are cancelled and have no effect as pertains to their use in cosmetics and externally applied drugs after January 29, 1990. Certificates issued for FD&C Red No. 3 lakes and all mixtures containing these lakes are cancelled and have no effect as pertains to their use in food, drugs, and cosmetics after January 29, 1990. Certificates issued for D&C Red No. 3 lakes and all mixtures containing those lakes are cancelled and have no effect as pertains to their use in drugs and cosmetics after January 29, 1990. Use of this color additive in the manufacture of cosmetics and of externally applied drugs and any use of the lakes of FD&C Red No. 3 (including the lakes of D&C Red No. 3) after this date will result in adulteration.

(2) The agency finds, on the scientific evidence before it, that no action must be taken to remove from the market food, drugs,

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and cosmetics to which the provisionally listed color additive or its lakes were added on or before January 29, 1990.

**PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS**

6. The authority citation for 21 CFR part 82 continues to read as follows:

Authority: Secs. 701, 706 of the Federal Food, Drug, and Cosmetic Act ([21 U.S.C. 371](#), [376](#), [376](#) note).

**§ 82.303 [Removed]**

7. Section 82.303 FD&C Red No. 3 is removed.

Dated: January 26, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

[FR Doc. 90-2265 Filed 1-29-90; 11:20 am]

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Part III

Department of Transportation

Federal Highway Administration

49 CFR Part 391

Controlled Substances Testing; Interim Final Rule; Request for Comments

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