(a) Influence or attempt to influence in any respect the loan and credit decisions or policies of [ ], the pricing of services, any personnel decisions, the location of any offices, branching, the hours of operation or similar activities of [ ];

(b) Influence or attempt to influence the dividend policies and practices of [ ] or any decisions or policies of [ ] as to the offering or exchange of any securities;

(c) Seek to amend, or otherwise take action to change, the bylaws, articles of incorporation, or character of [ ];

(d) Exercise, or attempt to exercise, directly or indirectly, control or a controlling influence over the management, policies or business operations of [ ]; or

(e) Seek or accept access to any non-public information concerning [ ].

B. [ ] is not a party to any agreement with [ ].

C. [ ] shall not assist, aid or abet any of [ ]'s affiliates or associates that are not parties to this Agreement to act, or act in concert with any person or company, in a manner which is inconsistent with the terms hereof or which constitutes an attempt to evade the requirements of this Agreement.

D. Any amendment to this Agreement shall only be proposed in connection with an amended rebuttal filed by [ ] with the FSLIC for its determination or a determination pursuant to delegated authority;

E. Prior to to acquisition of any shares of "Voting Stock" of [ ] as defined in the Regulation in excess of the Additional Shares, any required filing will be made by [ ] under the Control Act or the Holding Company Act and either approval of the acquisition under the Holding Company Act shall be obtained from the FSLIC or any Notice filed under the Control Act shall be cleared in accordance with the Regulations;

F. At any time during the 10 percent or more of any class of Voting Stock of [ ] is owned or controlled by [ ], no action which is inconsistent with the provisions of this Agreement shall be taken by [ ] until [ ] files and either obtains from the FSLIC a favorable determination with respect to either an amended rebuttal, approval of an Application under the Holding Company Act, or clearance of a Notice under the Control Act, in accordance with the Regulations;

G. Where any amended rebuttal filed by [ ] is denied or disapproved, [ ] shall take no action which is inconsistent with the terms of this Agreement, except after either (1) reducing the amount of shares of Voting Stock of [ ] owned or controlled by [ ] to an amount under 10 percent of a class of Voting Stock, or immediately ceasing any other actions that give rise to a conclusive or rebuttable determination of control under the Regulations; or (2) filing a Notice under the Control Act, or an Application under the Holding Company Act, as appropriate, and either obtaining approval of the Application or clearance of the Notice, in accordance with the Regulations;

H. Where any Application or Notice filed by [ ] is disapproved, [ ] shall take no action which is inconsistent with the terms of this Agreement, except after reducing the amount of shares of Voting Stock of [ ] owned or controlled by [ ] to an amount under 10 percent of any class of Voting Stock, or immediately ceasing any other actions that give rise to a conclusive or rebuttable determination of control under the Regulations;

I. Should circumstances beyond [ ]'s control result in [ ] being placed in a position to direct the management or policies of [ ], then [ ] shall either (1) promptly file an Application under the Holding Company Act or a Notice under the Control Act, as appropriate, and take no affirmative steps to enlarge that control pending either a final determination with respect to the Application or Notice, or (2) promptly reduce the amount of shares of [ ] Voting Stock owned or controlled by [ ] to an amount under 10 percent of any class of Voting Stock or immediately cease any actions that give rise to a conclusive or rebuttable determination of control under the Regulation;

J. By entering into this Agreement and by offering it for reliance in reaching a decision on the request to rebut the presumption of control under the Regulations, as long as 10 percent or more of any class of Voting Stock of [ ] is owned or controlled, directly or indirectly, by [ ], and [ ] possesses any Control Factor as defined in the Regulations, [ ] will submit to the jurisdiction of the Regulations, including (1) the filing of an amended rebuttal or Application or Notice for any proposed action which is prohibited by this Agreement, and (2) the provisions relating to a penalty for any person who willfully violates the [Holding Company Act or Control Act] and the Regulations thereunder, and any regulation or order issued by the FSLIC.

K. Any violation of this Agreement shall be deemed to be a violation of the [Holding Company Act or Control Act] and the Regulations, and shall be subject to such remedies and procedures as are provided in the [Holding Company Act or Control Act] and the Regulations for a violation thereunder and in addition shall be subject to any such additional remedies and procedures as are provided under any other applicable statutes or regulations for a violation, willful or otherwise, of any agreement entered into with the FSLIC.

III. This Agreement may be executed in one or more counterparts, each of which shall be deemed an original but all of which counterparts collectively shall constitute one instrument representing the Agreement among the parties thereto. It shall not be necessary that any one counterpart be signed by all of the parties hereto as long as each of the parties has signed at least one counterpart.

IV. This Agreement shall be interpreted in a manner consistent with the provisions of the Rules and Regulations of the Board.

V. This Agreement shall terminate upon (i) the approval by the Board of [ ]'s Application under the Holding Company Act or clearance by the Board of [ ]'s Notice under the Control Act to acquire [ ], and consummation of the transaction as described in such Application or Notice, or in the disposition by [ ] of a sufficient number of shares of [ ], or the taking of such other action that thereafter [ ] is not in control and would not be determined to be in control of [ ] under the Control Act, the Holding Company Act or the Regulations of the Board under either in effect at that time.

VI. IN WITNESS THEREOF, the parties thereto have executed this Agreement by their duly authorized officer.

[Acquiror]

Federal Savings and Loan Insurance Corporation.

Date: _____

By: _____

By the Federal Home Loan Bank Board.

John F. Ghizzoni,

Assistant Secretary.

[FR Doc. 88-19572 Filed 8-29-88; 8:45 am]

BILLING CODE 6720-01-M

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

14 CFR Part 1201

Statement of Organization and General Information

AGENCY: National Aeronautics and Space Administration (NASA).

ACTION: Final rule.

SUMMARY: NASA is amending 14 CFR Part 1201, "Statement of Organization and General Information," to reflect the current organizational structure and to make editorial corrections. This regulation sets forth NASA's policy and functions as established by the National Aeronautics and Space Act of 1958, as amended.

EFFECTIVE DATE: August 30, 1988.

ADDRESS: General Management Division, Code NPN-1, NASA Headquarters, Washington, DC 20546.

FOR FURTHER INFORMATION CONTACT: Margaret M. Herring, 20.2 453-2922.

SUPPLEMENTARY INFORMATION: NASA is revising §§ 1201.200 and 1201.400 to reflect the current organizational structure and to make editorial corrections. In § 1201.200(a)(1) the position title "Associate Deputy Administrator (Policy)" is changed to "Associate Deputy Administrator." § 1201.200(a)(3) is rewritten for clarification. § 1201.200(b)(8) is changed from the National Space Technology Laboratories to the John C. Stennis Space Center, Stennis Space Center, MS 39529. A correction is also made to § 1201.400(c) which corrects "48 U.S.C." to "48 CFR."

Since this revision involves internal administrative decisions and editorial changes, no public comment period is required.

The National Aeronautics and Space Administration has determined that:

1. This rule is not subject to the requirements of the Regulatory Flexibility Act, 5 U.S.C. 601-612, since it will not exert a significant economic impact on a substantial number of small entities.

2. This rule is not a major rule as defined in Executive Order 12291.

List of Subjects in 14 CFR Part 1201

Organization and functions (Goverment agencies).

For reasons set forth in the Preamble, 14 CFR Part 1201 is amended as follows:

PART 1201—STATEMENT OF ORGANIZATION AND GENERAL INFORMATION

1. The authority citation for 14 CFR Part 1201 continues to read as follows:

Authority: 5 U.S.C. 552, as amended.

2. Section 1201.200 is amended by revising paragraphs (a)(1), (a)(3), and (c)(8) to read as follows:

§ 1201.200 General.

(a) * * *

(1) The Office of the Administrator which includes the Administrator, Deputy Administrator, Associate Deputy Administrator, Associate Deputy Administrator (Institution), Assistant Deputy Administrator, and the Executive Officer.

* * * * *

(3) Fourteen Headquarters Offices. Thirteen of these offices provide agencywide leadership in certain administrative and specialized areas and one office provides administrative operations for Headquarters. All of these offices report directly to the Office of the Administrator.

* * * * *

(c) * * *

(8) John C. Stennis Space Center, Stennis Space Center, MS 39529.

* * * * *

3. Section 1201.400 is amended by revising paragraph (c) to read as follows:

§ 1201.400 NASA procurement program.

* * * * *

(c) All procurements are made in accordance with the Federal Acquisition Regulation (FAR) (48 CFR Chapter 1) and the Federal Acquisition Regulation Supplement (NASA/FAR Supplement) (48 CFR Chapter 18). Copies of these publications are available from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402, on an annual subscription basis.

James C. Fletcher,

Administrator.

August 23, 1988.

[FR Doc. 88-19674 Filed 8-29-88; 8:45 am]

BILLING CODE 7510-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 74, 81, and 82

[Docket No. 87N-0160]

D&C Red No. 33

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDS) is permanently listing D&C Red No. 33 for general use in drugs and cosmetics, except for use in the area of the eye. This action is in response to petitions filed by several petitioners. This rule will remove D&C Red No. 33 from the provisional list of color additives for general use in drugs and cosmetics.

DATES: Effective September 30, 1988, except for any provisions that may be stayed by the filing of proper objections; written objections and requests for a hearing by September 29, 1988.

ADDRESS: Written objections may be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Patricia J. McLaughlin, Center for Food Safety and Applied Nutrition (HFF-330), Food and Drug Administration, 200 C Street SW., Washington, DC 20204, 202-472-5740.

SUPPLEMENTARY INFORMATION:

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I. Introduction

In 1960, Congress passed the Color Additive Amendments (the amendments). In *Certified Color Mfg. Ass'n* v. *Mathews*, 543 F.2d 284, 286–287 (D.C. Cir. 1976), the United States Court of Appeals for the District of Columbia Circuit explained the purpose of this legislation:

> The Color Additive Amendments of 1960 reflect a Congressional and administrative response to the need in contemporary society for a scientifically and administratively sound basis for determining the safety of artificial color additives, widely used for coloring food, drugs, and cosmetics. The Amendments reflect a general unwillingness to allow widespread use of such products in the absence of scientific information on the effect of these products on the human body. The previously used system had some glaring deficiencies, and the 1960 Amendments were designed to overcome them. * * *
>
> (Footnotes omitted)

As amended, section 706(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376(a)) provides that a color additive will be deemed unsafe for use in food, drugs, cosmetics, and some medical devices unless FDA has issued a regulation permanently listing that color additive for its intended use. FDA will issue such a regulation only if it has been presented with data that establish with reasonable certainty that no harm will result from the use of the color additive. The burden of presenting such data is on the person who is seeking approval of the use of the additive.

In passing the amendments, Congress provided for the provisional listing of the color additives in use at that time, pending completion of the scientific investigations needed for a determination about the safety of these additives (section 203(b) of the transitional provisions of the amendments, Title II, Pub. L. 86–618, 74 Stat. 404–407 (21 U.S.C. 376, note)). Section 81.1 (21 CFR 81.1) of the agency's color additive regulations enumerates those color additives that are still provisionally listed. Among them is D&C Red No. 33 for use in drugs and cosmetics.

II. Regulatory History

A. The Color Additive

D&C Red No. 33, a dull bluish red dye of the monoazo class, is identified in *Chemical Abstracts* as the disodium salt of 5-amino-4-hydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid (CAS Reg. No. 3567–66–6). It is indentified in § 82.1333 (21 CFR 82.1333) as the disodium salt of 8-amino-2-phenylazo-1-naphtol-3,6-disulfonic acid. Other names include Colour Index Food Red 12 (C.I. No. 17200), C.I. Acid Red 33, Fast Acid Magenta B, and Acid Fuchsin D.

In manufacturing the additive, the product obtained from the nitrous acid diazotization of aniline is coupled with 4-hydroxy-5-amino-2,7-naphthalenedisulfonic acid in a alkaline aqueous medium. D&C Red No. 33 is soluble in water and glycerol and slightly soluble in methanol and ethanol.

D&C Red No. 33 is used in ingested drug preparations and in cosmetics subject to ingestion, such as lipsticks, dentifrices, mouthwashes, and breath fresheners. It is also used in externally applied cosmetics such as noncoloring hair preparations, skin care, fragrance, and make-up products.

The color additive D&C Red No. 33 has been in use for many years. Because D&C Red No. 33 was in use at the time the Color Additive Amendments of 1960 were enacted, it was provisionally listed for drug and cosmetic use in the **Federal Register** of October 12, 1960 (25 FR 9759).

In the **Federal Register** of October 12, 1960 (25 FR 9759), the agency established temporary tolerances for the provisional listing of certain color additives, including D&C Red No. 33, for use in lipsticks, ingested drugs, and other products subject to ingestion, such as mouthwashes and dentifrices. The original temporary tolerances, based on preliminary usage information and toxicity data available at that time, were intended to limit use of the color additive to safe levels until all required toxicity tests were completed. The agency has revised the temporary tolerances over the years as additional data became available, the lastest revision being on August 21, 1979 (44 FR 48964). D&C Red No. 33 usage is limited under the temporary tolerances in 21 CFR 81.25 to 3.0 percent by weight in lip cosmetics, to 0.75 milligram (mg) per daily dose of drugs, and to amounts consistent with current good manufacturing practice in mouthwashes and dentifrices.

Between 1960 and February 4, 1977, FDA postponed the closing date for the provisional listing of D&C Red No. 33 several times. The agency granted these postponements in response to requests for additional time to complete the scientific investigations necessary for listing the color additive under section 706 of the act.

B. Color Additive Petitions

In the **Federal Register** of November 20, 1968 (33 FR 17205), FDA announced that a petition (CAP 8C0086) for the permanent listing of D&C Red No. 33 as a color additive for use in ingested drugs, lipsticks, and externally applied drugs and cosmetics had been filed by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry and Fragrance Association (CTFA)), the Pharmaceutical Manufacturers Association (PMA), and the Certified Color Industry Committee (now the Certified Color Manufacturers Association, Inc. (CCMA)), c/o Hazleton Laboratories, Inc., P.O. Box 30, Falls Church, VA 22046 (now 9200 Leesburg Turnpike, Vienna, VA 22180).

The petition was filed under section 706 of the act (21 U.S.C. 376). A later notice (41 FR 9584; March 5, 1976) amended the notice of filing of the petition to include the use of D&C Red No. 33 in all types of cosmetics subject to ingestion and the additional use of D&C Red No. 33 in cosmetics intended for use in the area of the eye.

FDA notified the petitioners by letters dated May 14, 1976, August 15, 1977, and August 4, 1978, of the need for data to support the use of D&C Red No. 33 in cosmetics intended for use in the area of the eye. In a fourth letter, dated October 24, 1978, FDA advised the petitioners to consider withdrawing the portion of the petition that sought approval of the use of D&C Red No. 33 in cosmetics intended for use in the area of the eye because it appeared that the required data from eye-area studies were not readily available.

The petitioners have not submitted the required data on eye-area use. Therefore, FDA considers that portion of the petition that relates to the listing of D&C Red No. 33 for eye-area use to be withdrawn without prejudice in accordance with the provisions of § 71.4

(21 CFR 71.4). Use of D&C Red No. 33 in the area of the eye has never been covered by the provisional listing of this color additive.

The petitioners for CAP 8C0086 originally requested a regulation permitting up to 5.5 mg of D&C Red No. 33 per daily dose in ingested drugs, up to 3 percent of the color additive in cosmetics subject to ingestion, and use in amounts consistent with current good manufacturing practice in other cosmetics and topically applied drugs.

In February 1988, the petitioners amended their proposed tolerances to request that use of D&C Red No. 33 be limited to 0.75 mg per daily dose in ingested drugs. These uses and limitations are the same as the current uses and limitations under the provisional listing of this color additive.

In the **Federal Register** of August 6, 1973 (38 FR 21200), FDA announced that a petition (CAP 7C0059) for the permanent listing of D&C Red No. 33 as a color additive for use in drugs and cosmetics for external applications also had been filed by the Procter and Gamble Co., Toilet Goods Division, 6000 Center Hill Rd., Cincinnati, OH 45224. The petition was filed under section 706 of the act (21 U.S.C. 376).

C. Toxicological Testing of D&C Red No. 33

In the **Federal Register** of February 4, 1977 (42 FR 6992), FDA published revised regulations that required new chronic toxicity studies on 31 color additives, including D&C Red No. 33, as a condition for continued provisional listing for ingested uses. FDA required the new toxicity studies because the earlier toxicity studies that the petitioners had submitted to support the safe use of these color additives were deficient in several respects. FDA described these deficiencies in the **Federal Register** of September 23, 1976 (41 FR 41860):

1. Many of the studies were conducted using groups of animals, i.e., control and those fed the color additive, that are too small to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color. The small number of animals used does not, in and of itself, cause this result, but when considered together with the other deficiencies in this listing, does do so. By and large, the studies used 25 animals in each group; today FDA recommends using at least 50 animals per group.

2. In a number of the studies, the number of animals surviving to a meaningful age was inadequate to permit conclusions to be drawn today on the chronic toxicity or carcinogenic potential of the color additives tested.

3. In a number of the studies, an insufficient number of animals was reviewed histologically.

4. In a number of the studies, an insufficient number of tissues was examined in those animals selected for pathology.

5. In a number of the studies, lesions or tumors detected under gross examination were not examined microscopically.

In the February 4, 1977 rule, FDA postponed the closing date for the provisional listing of the color additives until January 31, 1981, for the completion of required toxicity studies. Subsequently, FDA published amendments to the provisional regulations in the **Federal Register** of April 7, 1978 (43 FR 14642), that required a new multigeneration reproduction study for D&C Red No. 33 as another condition of its continued provisional listing. The deficiency in the reproduction study previously submitted by the petitioners to support the safe use of the color additive was described in the **Federal Register** of December 13, 1977 (42 FR 62497; Docket No. 76N–0366). FDA found the study to be inadequate for assessing the potential for the color additive to affect reproduction adversely following ingestion. The selection of test animals for the succeeding generations was not made randomly, introducing a possible bias in the outcome of the studies. Evaluation of weaning weights of the animals to be used for subsequent generations disclosed that heavier, and, therefore, presumably healthier, test animals were selected in more instances than would have been dictated by random selection. This is an improper manner of selection as test animals selected for subsequent breeding should be representative of the available animals as a whole. The possible bias that was introduced by not selecting animals randomly but rather by weight may have resulted in the nonselection of animals exhibiting adverse effects.

In the **Federal Register** of March 27, 1981 (46 FR 18954), FDA established the closing date of March 31, 1983, for the completion of the evaluation of D&C Red No. 33. Because its review of the data and of the scientific and legal issues raised on this color additive took longer than the agency anticipated, FDA had to extend the provisional listing of the color additive on a number of occasions. On June 26, 1985 (50 FR 26377), FDA proposed a longer extension of the provisional listing for several color additives, including D&C Red No. 33, to provide for the submission of additional information. On September 4, 1985 (50 FR 35783), the agency published a final rule extending the provisional listing for D&C Red No. 33 until March 3, 1987. On July 30, 1986, CTFA submitted additional information, which is discussed below. To provide time for the completion of its review and preparation of the appropriate documents, the agency further extended the closing date several times. The most recent extension was announced in the **Federal Register** on July 1, 1988 (53 FR 25127), establishing the current closing data of August 30, 1988.

d. Citizen Petition Filed by Public Citizen Health Research Group

On December 17, 1984, the Public Citizen Health Research Group (Public Citizen) petitioned FDA to ban the use of the color additives that remained provisionally listed. On January 22, 1985, Public Citizen filed a complaint in the District Court for the District of Columbia seeking the same relief. Public Citizen alleged that, by continuing to provisionally list the color additives, including D&C Red No. 33, FDA had violated the Color Additive Amendments to the act, as well as those provisions of the Administrative Procedure Act (5 U.S.C. 706(1)) that pertain to unreasonable delay of agency action. Public Citizen sought to enjoin FDA from using the provisional list or any other means to allow the marketing of the provisionally listed color additives.

On June 21, 1985, the Commissioner of Food and Drugs sent to Public Citizen a detailed response to the petition. In his response, the Commissioner carefully reviewed and discussed the arguments and information submitted in support of the petition. The Commissioner concluded that the public health would not be endangered by the continued marketing of the color additives while scientific, legal, and policy issues were addressed and, therefore, the Commissioner denied the petition.

On February 13, 1986, Judge Stanley S. Harris granted FDA's motion for summary judgment and dismissed Public Citizen's complaint. *Public Citizen, et al. v. DHHS, et al.*, No. 85–1573 (D.D.C. February 13, 1986). Public Citizen's appeal of this decision was denied by the U.S. Court of Appeals, No. 86–5150 (October 23, 1987).

III. Evaluation of the Safety of D&C Red No. 33

A. *Statutory Safety Requirements*

Under section 706(b)(4) of the act (21 U.S.C. 376 (b)(4)), the so-called "general safety clause" for color additives, a color additive cannot be listed for a particular use unless the data presented to FDA establish that it is safe for that use. Although what is meant by "safe" is not explained in the general safety clause, the legislative history makes clear that this word is to have the same

meaning for color additives as for food additives. (See H. Rept. No. 1761, "Color Additive Amendments of 1960," Committee on Interstate and Foreign Commerce, 86th Cong., 2d Sess. 11 (1960).) The Senate report on the Food Additives Amendment of 1958 states:

> The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstances.
>
> This was emphasized particularly by the scientific panel which testified before the subcommittee. The scientists pointed out that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of any chemical substance.

S. Rept. No. 2422, "Food Additives Amendment of 1958," Committee on Labor and Public Welfare, 85th Cong., 2d Sess. 6 (1958).

FDA has incorporated this concept of safety into its color additive regulations. Under 21 CFR 70.3(i), a color additive is "safe" if "there is convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive." Therefore, the general safety clause prohibits approval of a color additive if doubts about the safety of the additive for a particular use are not resolved to an acceptable level in the minds of competent scientists.

The general safety clause is buttressed by the anticancer or Delaney clause (section 706(b)(5)(B) of the act), which provides that a color additive shall be deemed to be unsafe "for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal," and it shall be deemed unsafe "for any use which will not result in ingestion of any part of such additive, if, after tests which are appropriate for the evaluation of the safety of additives for such use, or after other relevant exposure of man or animal to such additive, it is found by the Secretary to induce cancer in man or animal" (21 U.S.C. 376(b)(5)(B)).

The application of the Delaney clause to color additives was amplified recently by a decision concerning D&C Orange No. 17 and D&C Red No. 19 in *Public Citizen, et al.* v. *Young, et al.* (D.C. Cir. No. 86–1548, October 23, 1987):

> In sum, we hold that the Delaney Clause of the Color Additive Amendments does not contain an implicit *de minimis* exception for carcinogenic dyes with trivial risks to humans. We based this decision on our understanding that Congress adopted an "extraordinarily rigid" position, denying the FDA authority to list a dye once it found it to "induce cancer in * * * animals" in the conventional sense of the term.

B. Earlier Studies

Among the earlier toxicity studies on the color additive, submitted by the petitioners before 1977, were acute oral toxicity studies in rats, dogs, and mice; short-term and chronic feeding studies in dogs and rats; a three-generation reproduction study in rats; teratology studies in rats and rabbits; dermal studies in rabbits; and 2-year skin-painting studies in mice. Some toxic effects, including hemolytic anemia and enlarged spleens, were observed at higher doses in the pre-1977 feeding studies, but the agency concluded that the color additive could be used safely until the completion of further testing.

From the earlier studies with D&C Red No. 33 submitted by the petitioners, the agency has evaluated the dermal safety of the color additive. The data from these studies demonstrate that D&G Red No. 33 is nonirritating when applied repeatedly to either intact or abraded skin. Furthermore, D&C Red No. 33 was not found to be carcinogenic in two studies in which it was applied periodically to the skin of mice over their lifetimes.

FDA has evaluated the genetic toxicity tests related to D&C Red No. 33 found in the literature. The available information is fragmentary and inconsistent, and the agency considers the full complement of animal toxicity studies to provide more pertinent information on safety than these in vitro tests. FDA finds no basis for further concerns in this information.

C. New Studies

In the new reproduction study required by the April 7, 1978, order, Sprague-Dawley (Charles River) COBS CD rats were fed dietary levels of 0, 0.25, 2.5, 7.5, and 25 milligrams per kilogram (mg/kg) per day of D&C Red No. 33. Twenty females and 20 males for each group were used to initiate the study, which was conducted for three generations. The selection of test animals for the succeeding generations was made randomly. Examination of a number of indices of viability, health, reproductive abnormality, and developmental toxicity in offspring and mothers did not reveal any pattern of adverse effects. From evaluation of the new multigeneration reproduction study in rats and of earlier teratology studies, agency scientists have concluded that there have been no reproductive or teratogenic effects related to treatment with the color additive.

Reports were submitted to FDA on the new chronic toxicity studies in rats and mice required by the February 4, 1977, order. These new studies represent current state-of-the-art toxicological testing. The protocols for these studies have benefited from knowledge of deficiencies in previously conducted carcinogenesis bioassays and other chronic toxicity protocols. The use of large numbers of animals of both sexes, pilot studies to determine maximum tolerated dosages, two control groups (thereby effectively doubling the number of controls), and in utero exposure in one of the two species tested, significantly increase the power of these tests to detect dose-related effects.

The reproduction and chronic studies were conducted for the petitioner by International Research and Development Corp., Mattawan, MI 49071. The color additive fed to the animals in theses studies contained 88 percent total color.

In the new chronic mouse study, D&C Red No. 33 was fed to Charles River CD–1 mice at dietary levels of 0, 0.1, 1, and 5 percent. Sixty females and 60 males were used for each dietary level and in each of 2 control groups. The male mice fed 5 percent D&C Red No. 33 were sacrificed at 57 weeks and the female mice fed 5 percent were sacrificed at 74 weeks due to reduced survival. All other groups were sacrificed at 104 weeks of feeding. The mice fed 1 and 5 percent of D&C Red No. 33, compared to the controls, showed hemolytic anemia and associated adverse effects, but no adverse effects were seen in mice fed 0.1 percent. No increased incidence of tumors was related to feeding of the test substance. Based on the evaluation of the results of this chronic mouse toxicity study, the agency has determined that D&C Red No. 33 did not cause cancer in Charles River CD–1 mice.

In one chronic study, Sprague-Dawley (Charles River CD) rats were fed dietary levels of 0, 0.25, 0.05, and 0.2 percent D&C Red No. 33 for 129 weeks. These rats were exposed in utero and during lactation by the feeding of the same dietary levels of D&C Red No. 33 to their parents. Seventy females and 70 males were used for each dietary level and in each of 2 control groups.

A related second study was performed with the same strain of rats, in which the animals, similarly exposed in utero and during lactation, were fed

either 0 or 2 percent of D&C Red No. 33. FDA requested that this feeding level be added to provide testing at the highest level compatible with completion of the test. The agency's analysis of data from earlier studies suggested that this maximum level of 2 percent could be used without jeopardizing completion of the study. The males were sacrificed at 113 weeks of feeding and the females at 117 weeks. There were 70 animals of each sex in each group.

Tests rats in both studies showed adverse effects associated with hemolytic anemia. Decreases in erythrocyte counts, decreases in hemoglobin levels, and increases in reticulocyte counts were seen at the 0.2 percent and the 2 percent doses. Also at the 0.2 percent dose, the males had increased spleen/body weight ratios at the 12-month sacrifice and the females had increased spleen weights at the end of the study. No adverse effects were seen at the 0.05 percent level or below.

In the second rat study, survival of males fed 2.0 percent was less than the controls and the body weights of treated rats were decreased compared to controls. The treated rats of both sexes showed enlargement of the spleen at 12 months and also at termination of the study. Both sexes of the treated group showed a marked increase in parenchymal fibrosis of the spleen compared to their controls. Both sexes also had splenic capsular fibrosis, and, in addition, the males showed fatty metamorphosis. In the spleens of the 140 treated rats, the agency also found a few uncommon tumors: three fibrosarcomas and one hemangioma in males and one fibroma in females. One male control rat had a hemangiosarcoma. The incidences of the various tumors are not sufficient to show carcinogenicity. Based on the evaluation of the results of both chronic rat studies, the agency has determined that D&C Red No. 33 did not cause cancer in Sprague-Dawley rats.

D. The Issue of Whether More Testing is Necessary

1. *Statement of the issue.* In a notice of proposed rulemaking (50 FR 26377; June 26, 1985), FDA stated that the chronic testing of both D&C Red No. 33 and D&C Red No. 36 did not reveal a carcinogenic effect in the animals in which they were tested. FDA noted increased incidences of unusual, nonneoplastic splenic lesions in Sprague-Dawley rats fed high doses of D&C Red No. 33. There were higher incidences of parenchymal fibrosis, enlargement, capsular fibrosis, and (in males) fatty metamorphosis of the spleen in animals fed the test compound than in the control animals. In the 140 rats fed D&C Red No. 33 there were three fibrosarcomas, one hemangioma, and one fibroma.

In the proposal, FDA stated that if it had only results of the testing of D&C Red No. 33 and D&C Red No. 36 before it, the agency would likely have approved the use of these color additives in spite of the observed effects. However, the proliferative effects seen in the testing of D&C Red No. 33 and D&C Red No. 36 indicated to FDA that there was a similarity between these color additives and certain other compounds, such as D&C Red No. 9, that have been shown to be carcinogenic. When D&C Red No. 9 was fed to Sprague-Dawley rats, a few rare tumors and numerous rare lesions of the spleen were produced. These rats had the same kinds of nonneoplastic lesions as with D&C Red No. 33 and D&C Red No. 36. When D&C Red No. 9 was fed to Fischer 344 rats, however, numerous rare tumors of the spleen were produced, and D&C Red No. 9 was found to be a splenic carcinogen in this strain.

The association of the nonneoplastic splenic lesions with tumor occurrence suggested to FDA that the nonneoplastic lesions may be precursors or indicators of the start of a carcinogenic process. This similarity of effects in the Sprague-Dawley strain of rats between D&C Red No. 33, on the one hand, and D&C Red No. 9, on the other, raised concerns that D&C Red No. 33 may be carcinogenic in the Fischer 344 rat. To clarify the significance of this similarity of effects, FDA proposed that new studies be conducted on D&C Red No. 33 and D&C Red No. 36 (50 FR 26377; June 26, 1985). The agency stated that it believed that such studies would be the best way to resolve the ambiguities about these color additives that had been created by the results of the testing with D&C Red No. 9 and other compounds in Fischer 344 rats. The agency also noted, however, that it would reconsider the issue of additional testing if data and information were received that showed that such testing was not necessary.

As part of its effort to resolve this problem, FDA, in 1984, had asked that a panel of experts from the National Toxicology Program's Board of Scientific Counselors examine the data on D&C Red No. 33 in conjunction with the data on D&C Red No. 9. FDA sought the guidance of the Board on two questions: "(1) Do the results of the long-term feeding studies of D&C Red No. 33 in CD–1 (Charles River) mice and Sprague-Dawley (Charles River) rats indicate a possible carcinogenic effect that could be attributed to exposure to this color additive? (2) In particular, do the splenic changes in rats constitute evidence of neoplastic potential?"

The Board met on July 26, 1984, and provided the following response:

1. Quantitatively, the low incidence rates for primary mesenchymal neoplasms of the spleen in male and female Charles River CD–1 rats given long term dietary administration of 2% D&C Red No. 33 could not be considered sufficient to be categorized as a demonstrated carcinogenic response to chemical treatment.

2. Qualitatively, there appears to be treatment-related nonneoplastic target organ (spleen) toxic responses which are similar to those previously described for certain other aromatic azo compounds, aromatic nitro compounds, and amines.

3. Further research is necessary and should be directed toward developing understanding of the mechanisms of the toxic action of this particular family of compounds in the spleen of rats. (Ref. 1).

FDA agrees with the Board's first point and concludes that the evidence does not establish D&C Red No. 33 to be a carcinogen. The incidences of splenic tumors in Sprague-Dawley rats (produced by Charles River) do not show carcinogenicity.

The agency agrees with the Board's second point, that there were similar nonneoplastic splenic effects produced with D&C Red No. 33 as there were with others in this family of compounds. FDA acted on this basis in publishing the proposal on June 26, 1985 (50 FR 26377).

The Board's third recommendation was intended to apply to the narrow question of what is needed to further scientific understanding, and not what is needed to protect the public health.

The petitioners' comments on the 1985 proposal suggested that conducting a risk assessment based on the comparative toxicities of D&C Red No. 9, D&C Red No. 33, and D&C Red No. 36 in Sprague-Dawley rats would show that additional testing would not be necessary to protect the public health. The petitioner later submitted a lengthy comparative assessment on the relative splenic toxicities of the three color additives.

2. *Resolution of the issue.* The agency carefully considered the petitioners' comments and concluded that, if the splenic toxicity associated with the use of these color additives were produced by the major components of the colors, then it should be possible to evaluate the health concern raised by the color additives using the data from the studies involving the Sprague-Dawley rat and the D&C Red No. 9 study in the Fischer 344 rat. FDA concluded that knowledge of the relative toxicities of these additives would enable the agency to make a determination about the safety

of D&C Red No. 33 and D&C Red No. 36 without requiring new long-term studies (50 FR 35783 at 35788; September 4, 1985).

FDA has conducted its own comparative evaluation based on the relative toxicities of D&C Red No. 9 and D&C Red No. 33 (Ref. 2). The assessment shows that, even assuming that D&C Red No. 33 were carcinogenic if subjected to further testing in a strain of rat other than the Sprague-Dawley, the theoretical, upper-bound, lifetime risk associated with exaggerated use exposure to the compound would be extremely small, that is, less than 3×10^{-7} (Ref. 3).

In light of this comparative evaluation, the agency has reconsidered whether additional chronic testing of D&C Red No. 33 is necessary to establish the safety of the compound. When deciding whether to require additional testing for a compound under review, the agency routinely follows the principle articulated in its toxicology guidelines that "the degree of effort expended in reducing uncertainty about the safety of an additive ought to relate in some concrete way to the likelihood that the substance poses a potential for health risk to the public * * *." (Ref. 4, p. 10). By showing that the splenic toxicity presents no reasonable likelihood of harm to the public, the assessment adequately responds to the agency's initial concern that additional testing of the additive would be necessary to protect the public health. In fact, in light of the assessment, to require additional testing would be pointless from a public health perspective and contrary to agency practice.

Accordingly, the agency concludes that the existing carcinogenicity studies concerning D&C Red No. 33 are adequate for the evaluation of the color additive.

E. Summary of the Safety Evidence for D&C Red No. 33

1. *Adequacy of the submitted studies to demonstrate safety.* The series of studies completed by the petitioner satisfies the usual requirements to demonstrate safety for a color additive that will be ingested and applied dermally. The studies were properly conducted and are acceptable under today's standards of toxicity testing. Agency scientists have found no adverse effects related to treatment with the color additive in doses up to the highest dose of 25 mg/kg in the teratology studies or in the 3-generation reproduction studies. The long-term studies in dogs, mice, and rats all showed the hemolytic anemia syndrome prominently at high doses. The highest dose level that did not show this syndrome was 150 mg/kg (0.1 percent) in mice, 12.5 mg/kg in dogs, and 25 mg/kg (0.05 percent) in rats. Thus, the safety studies established a no-observed-effect-level of 12.5 mg/kg body weight or higher in all species tested.

Based on its evaluation of these studies and on its analysis of concerns raised by studies on D&C Red No. 9, the agency concludes that the data show that no harm will result from using D&C Red No. 33 under the conditions prescribed.

2. *Negative results of carcinogenicity studies.* As discussed above, the agency believes that these studies are adequate to determine whether D&C Red No. 33 is carcinogenic. No significant increased incidence of any type of tumor, in any of the many tissues examined, in either sex, in any dose group, in any strain of any species tested, by either ingestion or skin application, was associated with D&C Red No. 33 treatment in any of the studies. Thus, after thorough evaluation of these studies, which meet modern design standards for tests to determine carcinogenicity, the agency finds that D&C Red No. 33 has not induced cancer in any of the laboratory testing. As stated above, the National Toxicology Program's Board of Scientific Counselors has also concluded that the data do not demonstrate a carcinogenic response to treatment. Accordingly, the Delaney clause is not applicable to the decision on this color additive.

3. *Conclusion.* For the foregoing reasons, the agency considers that the direct testing of D&C Red No. 33 show that the color additive is safe for use in drugs and cosmetics.

IV. Potential Carcinogenic Impurities

For the reasons discussed above, the agency considers that the direct testing of D&C Red No. 33 shows that the color additive is safe for use in drugs and cosmetics. The agency must still consider, however, any risk posed by possible carcinogenic impurities in D&C Red No. 33.

A. The Impurities Found

During the safety review, the agency developed a new analytical methodology for examining the color additive for the presence of trace level impurities. Analyses by this new methodology found six carcinogenic impurities in commercial, certified batches of D&C Red No. 33 (Refs. 5 and 6). The carcinogenic impurities that the agency detected are 4-aminoazobenzene, 4-aminobiphenyl, aniline, azobenzene, benzidine, and 1,3-diphenyltriazene. These impurities result from impurities in the starting materials used to manufacture the color additive, remaining traces of starting material, and from reactions involving these impurities during the manufacturing process. The regulation set forth below establishes specifications that would limit the concentrations of all six of these impurities in future batches.

Because of its concerns about the carcinogenic impurities, the agency has analyzed representative samples from 10 certified batches of the color additive (Refs. 5 and 6). The results of the analyses, expressed as concentration in parts per billion (ppb), for the 6 carcinogenic impurities in these 10 batches are summarized in Table I.

TABLE I.—LEVELS OF IMPURITIES FOUND IN D&C RED NO. 33

Impurity	No. of batches (out of 10)[a] containing detectable amounts of impurity	Range of impurity concentration (ppb) [b]	Average impurity level in 10 samples (ppb)[c]
4-Aminoazobenzene.	10	50–3, 100	500
4-Aminobiphenyl.	10	40–530	260
Aniline	10	2,000–19,900	8,300
Azobenzene	2	ND–2,200	410
Benzidine	4	ND–60	15
1,3-Diphenyltriazene.	8	ND–410	100

[a] Thirteen certified batches were analyzed but each batch was not necessarily analyzed for all six impurities. Ten batches were examined for each impurity.

[b] Approximately detectability limits: Azobenzene—200 ppb; Benzidine—1 ppb; 1,3-Diphenyltriazene—10 ppb.

[c] Impurity assumed to be present at detectability limit if not detected.

The detectability limit mentioned in the table is the approximate concentration of the impurity sufficient to cause a visible response on the chromatogram. This limit is lower than the concentration that will produce a response that can be reproducibly quantitated with good precision.

B. Prior Actions by FDA

The current testing of D&C Red No. 33 has not proven it to be a carcinogen, and, thus, the anticancer clause does not apply to it. Nevertheless, the agency must still consider whether the color additive, in light of the fact that it may contain carcinogenic impurities, may be safely used in drugs and cosmetics.

The agency is using the same approach for this situation concerning impurities in D&C Red No. 33 as it used to examine the risk associated with the presence of minor carcinogenic impurities in FD&C Yellow No. 5 (50 FR 35774; September 4, 1985), and FD&C Yellow No. 6 (51 FR 41765; November 19, 1986), both of which may contain the same impurities as those found in D&C Red No. 33. These color additives had not been shown to be carcinogenic by appropriate bioassays. FDA concluded that the use of each of these color additives, within prescribed specifications, is safe.

The agency's position is supported by *Scott* v. *FDA*, 728 F.2d 322 (6th Cir. 1984). That case involved a challenge to FDA's decision to approve the use of D&C Green No. 5 (47 FR 24278; June 4, 1982), which contains a carcinogenic chemical but has not itself been shown to cause cancer. Relying heavily on the reasoning in the agency's decision to list D&C Green No. 5, the United States Court of Appeals for the Sixth Circuit rejected the challenge to FDA's action and affirmed the listing regulations.

The assessment procedure used to estimate risk from an impurity has two aspects: (1) Assessment of the probable exposure to the impurity from the proposed use of the additive, and (2) extrapolation of carcinogenic potency observed in the animal bioassay with the impurity to the conditions of probable human exposure.

C. Exposure to Carcinogenic Impurities in D&C Red No. 33

The agency has estimated the maximum risk from exposure to the carcinogenic impurities that may result from use of D&C Red No. 33 in drugs and cosmetics. The lifetime exposure to D&C Red No. 33 is not expected to exceed 160 micrograms/person/day (θg/person/day) internally and 800 θg/person/day from dermal exposure, for the high users (Ref. 2). With these estimates, the agency has examined the likely exposures to the carcinogenic impurities in D&C Red No. 33.

In adopting specifications for D&C Red No. 33, FDA considered the concentrations of the carcinogenic impurities that were present in the certified batches of the color additive that the agency recently surveyed and in the batches used for the toxicological testing.

The agency believes that the specifications listed in the first column of Table II are readily obtainable under current good manufacturing practice and will assure safe use of the color additive.

TABLE II—ESTIMATED IMPURITY EXPOSURE AT THE SPECIFICATION LIMITS

Impurity	Specification (ppb)	High User Exposure (ng/day) [1] Systemic	Dermal
4-Aminoazobenzene	100	0.02	0.08
4-Aminobiphenyl	275	.04	.....
Aniline	25,000	4.0	.....
Azobenzene	1,000	.2	.....
Benzidine	20	.003	.....
1,3-Diphenyl-triazene	125	.02	.1

[1] ng=Nanograms (1 billionth of a gram).

Table II also gives the estimated high user exposure to the impurities if each batch of the color additive contained each impurity at the maximum level allowed by the specifications. The systemic exposure is calculated by multiplying the high user exposure for the color additive itself (160 θg/day by ingestion) by each specification. Systemic exposure to these impurities from dermal application will be negligible compared to ingestion because the major fraction of exposure to this color additive results from its ingested uses and because only a small fraction of a dermally applied product is likely to be absorbed.

Two of the impurities, 4-aminoazobenzene and 1,3-diphenyltriazene, have been shown not only to be systemic carcinogens when ingested but also to be skin carcinogens when applied dermally. Accordingly, for these two impurities, the agency has estimated the risks from dermal exposure as well as those from systemic exposure. FDA has based its estimates of dermal exposure on the high user exposure to D&C Red No. 33 (800 θg/day) multiplied by each specification (Ref. 7).

D. Risk Estimations for Impurities

The second part of the evaluation of the risk presented by the presence of the impurities is an extrapolation from the actual compound-related incidence of tumors found in animal bioassays, under conditions of exaggerated exposure, to the conditions of much lower probable exposure for humans.

The agency has used estimates of carcinogenic potency and estimates of exposures to the carcinogenic impurities for high users of D&C Red No. 33 (with all carcinogenic impurities at the maximum concentrations allowed by the specifications) to estimate risks for exposure to each impurity (Ref. 7). The agency then summed these risks to derive the maximum upper bound risk associated with lifetime exposure to D&C Red No. 33.

The agency searched the scientific literature for evidence on the carcinogenicity of the impurities found in D&C Red No. 33. If more than one study found one of these impurities to be carcinogenic, the agency identified the study that was most suitable to estimate risk. Although, in general, these studies were not designed to estimate risk and were often deficient under current standards, they are the only studies available and can not be ignored. Also, the reports did not always provide all the information necessary for a risk estimate. The agency has thus attempted to make assumptions and corrections that would provide estimates that are reasonable while not underestimating the risk. These assumptions and corrections are discussed more fully in the discussions of each constituent.

1. *4-Aminoazobenzene.* The agency has evaluated reports showing that 4-aminoazobenzene is carcinogenic in the diet of rats (Refs. 8 and 9), and that it is carcinogenic when applied dermally to rats (Ref. 10). The agency has developed a risk estimate from each of these studies.

A study implicating 4-aminoazobenzene as a carcinogen by dietary administration to Wistar rats was reported by Kirby et al. (Ref. 9). The study reported that 7 of the 16 animals in the treated group were found to have liver cell neoplasms after a total of 120 weeks. Six rats in this group displayed papillomas of the stomach. No information is available to determine whether any of the individual rats had neoplasms in both the liver and the stomach. The dose was allowed to vary throughout the experiment. The agency calculated the average dose over 120 weeks to be 0.25 percent in the diet (Ref. 11).

4-Aminoazobenzene was also implicated as a carcinogen in a skin painting study in which 1.0 milliliter (mL) of a 0.2 percent acetone solution containing 4-aminoazobenzene (corresponding to a dose of 2 mg of 4-aminoazobenzene per application) was applied to the skin twice weekly on six male albino rats. This was part of a larger study utilizing a number of azo compounds (Ref. 10). All six male rats in the treatment group displayed skin neoplasms after 123 weeks compared to none in the control group.

The agency has estimated that the lifetime risk of cancer from systemic exposure to 4-aminoazobenzene is less than 3 in 1 trillion from products containing D&C Red No. 33 (Refs. 5 and 11). The data indicate, however, that 4-aminoazobenzene may be a more potent carcinogen at the site of application to

the skin than when absorbed systemically. The agency has estimated that the lifetime risk of skin cancer from dermal application is less than 2 in 1 billion (Refs. 5 and 11). Because the risk estimate for dermally applied products is larger than for ingested products, FDA is using this higher estimate to evaluate total risk.

2. *4-Aminobiphenyl.* A number of studies in different species have been performed on 4-aminobiphenyl. The agency has chosen a dog study reported both by Block et al. and by Rippe et al. for quantitative risk assessment because the data on this study yield a higher risk estimate than data from other studies (Refs. 12, 13, and 14).

In this study, 24 pure-bred female beagle dogs were administered 4-aminobiphenyl orally, by capsule, at a dosage level of 5 mg/kg body weight for 5 days a week. Cystoscopic examinations were made routinely starting at 16 months and continuing up to 41 months after commencement of treatment. Diagnoses at 24 months showed that 22 of 24 treated dogs had bladder papillomas. Because this incidence is so high, data at later times show essentially the same incidence. Data at earlier times show a lower incidence, proportional to the lesser exposure time. The agency concludes that data obtained at 24 months are the most reliable for risk assessment because, among other reasons, more complete histopathology was performed at this time (Ref. 14).

Under circumstances in which lifetime risk must be estimated from studies that are performed for less than a lifetime, the data must be corrected to account for the fact that the animals were at risk for less than a lifetime. Typically, tumor incidence has been thought to be proportional to some power of time (Ref. 15). The agency believes that, in the absence of specific data, it is reasonable to make adjustments based on a model that uses the third power of the time exposed (Refs. 14 and 15).

Because 24 months represent approximately one-fifth of the lifetime of a beagle dog, the agency has corrected for the rapid induction of these neoplasms in the calculation of lifetime risk. Extrapolating directly from the data and making a correction for less than lifetime exposure, the agency estimates that the lifetime risk of cancer from systemic exposure to 4-aminobiphenyl in products containing D&C Red No. 33 is less than 2 in 100 million (Refs. 5 and 14).

3. *Aniline.* Data reported by the National Cancer Institute (NCI) demonstrated that aniline was carcinogenic to the spleen of Fischer 344 rats (Ref. 16). This finding has subsequently been verified by a dietary study performed by the Chemical Industry Institute of Toxicology (CIIT) using the same strain of rat (Ref. 17). FDA used data from the CIIT study to estimate that the lifetime risk of cancer from systemic exposure to aniline in products containing D&C Red No. 33 is less than 4 in 100 billion (Refs. 5 and 18).

4. *Azobenzene.* In an NCI-sponsored bioassay reported in 1979, azobenzene induced a dose-related increase in the incidence of sarcomas of the abdominal cavity, particularly the spleen, in both sexes of Fischer 344 rats (Ref. 19). Three groups of animals of both sexes were given 0, 200, and 400 parts per million (ppm) in the diet. From this study, the agency estimates that systemic exposure to azobenzene in products containing D&C Red No. 33 presents a lifetime risk of less than 2 in 100 billion (Refs. 6 and 20).

5. *Benzidene.* FDA used a human epidemiology study by Zavon (Ref. 21) and a study performed by Rinde and Troll in the rhesus monkey (Ref. 22) as the basis for a quantitative risk assessment on benzidine. Zavon attempted to obtain good data on exposure to benzidine by analyzing the urine of workers in a plant that manufactures this substance. The workers were monitored until a number of them were diagnosed as having bladder neoplasms. Urine levels of benzidine in workers were measured before each work shift, after each work shift, and on every Monday morning. Average levels were: before work, 0.01 milligram per liter (mg/L); after work, 0.04 mg/L; and on Monday morning before work, somewhat below 0.005 mg/L.

No controlled study with the administration of benzidine and the concomitant measurement of benzidine in the urine in humans has been performed. Thus, the conversion from urine concentration to total exposure cannot be made from human data alone. However, the Rinde and Troll study related ingestion of benzidine to amounts of benzidine and monoacetylbenzidine in the urine of rhesus monkeys. The agency believes it is reasonable to use this study to relate urine concentration to exposure for humans (Ref. 23). This procedure yields a higher risk estimate than if the risk was estimated solely from an animal feeding study and thus is less likely to underestimate risk.

In the Rinde and Troll study, benzidine was administered orally to rhesus monkeys, and the 72-hour urine collection was analyzed for benzidine and monoacetylbenzidine. In two trials the amount of benzidine and monoacetylbenzidine excreted in the urine was 1.4 percent and 1.5 percent of the initial input. The agency used these data, and applied a safety factor of two to compensate for uncertainties, to estimate that the amount of benzidine and monoacetylbenzidine excreted in the urine of humans is approximately 3 percent of that consumed. The agency then calculated that the average human worker in the Zavon study was exposed to approximately 0.8-mg benzidine per work day. Based on these two studies, the agency estimates that systemic exposure to benzidine from products containing D&C Red No. 33 presents a lifetime risk of less than 2 in 100 million (Refs. 5 and 23).

6. *1,-Diphenyltriazene.* The agency has evaluated reports showing that 1,3-diphenyltriazene is carcinogenic in the diet, and that it is carcinogenic when applied dermally. A study performed by Otsuka (Ref. 24), while deficient in certain aspects, showed that 1,3-diphenyltriazene produced forestomach tumors in mice upon dietary exposure. The compound was administered in the diet at a concentration of 0.04 percent for 483 days. Although this dietary study is quite old and was terminated after 16 months, the agency believes that it is usable if corrected for less than lifetime exposure. Assuming that the average lifetime of a mouse is 24 months, the agency has corrected for less than lifetime exposure by assuming the risk of cancer increases as the third power of the time exposed (Refs. 15 and 25). Therefore, the agency has used a correction factor of 3.4, i.e., (24 months/16 months) ^{3}, which increases the estimated risk.

Using this correction, the agency estimates that systemic exposure to 1,3-diphenyltriazene from products containing D&C Red No. 33 presents a lifetime risk of less than 4 in 1 trillion (Refs. 6 and 25).

A lifetime skin-painting study using 1,3-diphenyltriazene on mouse skin was performed by Kirby (Ref. 26). This skin study involved a thrice weekly application of a 5-percent solution of the test compound in acetone. In 16 mice surviving more than 300 days, 3 developed squamous cell papilloma and 3 developed squamous cell carcinoma. One mouse that developed a carcinoma could not be identified as part of this experiment or a parallel experiment. The agency has assumed that this mouse was part of this experiment so as not to underestimate risk. As was often the case in the 1940's, when this study was conducted, the amount of solution applied to the skin of the animals was

not accurately measured and thus not reported for this experiment. The failure to measure and to report this information creates problems in conducting a quantitative risk assessment. However, in later years, the standard protocol for this kind of study in mice became the application of 0.20 mL of solution to the skin. Because the agency does not know whether as much as 0.20 mL was applied, it has made a more conservative assumption that 0.10 mL was used in order to estimate the risk. Using this procedure, the agency estimates that dermal exposure to 1,3-diphenyltriazene from products containing D&C Red No. 33 presents a lifetime risk of less than 1 in 100 billion (Refs. 6 and 25).

E. Cumulative Risk Estimates

In evaluating FD&C Yellow No. 5, the agency established a procedure of setting specifications for more than one carcinogenic constituent for the same color additive (50 FR 35774; September 4, 1985). The agency used the same procedure when it evaluated the safety of FD&C Yellow No. 6 (51 FR 41765; November 19, 1986) and is using it again in evaluating the safety of D&C Red No. 33 because it is necessary to consider the most appropriate way to evaluate the risk from simultaneously consuming small amounts of several carcinogenic agents.

The Office of Science and Technology Policy discussed the issue of exposure to multiple carcinogenic agents in a document entitled "Chemical Carcinogens; A Review of the Science and Its Associated Principles" (50 FR 10371, 10394; March 14, 1985) as follows:

> Since people are exposed to many different agents at the different times in different sequences, the effect of multiple agents on carcinogenesis is of major concern. However there is little information of general import in the field. Models for interaction are generally limited by lack of information on dose-response curves for carcinogens in the area of interest. The great number of permutations of possible agents and doses makes understanding interaction of multiple agents very difficult.
>
> In general, the action of two or more agents can be additive (if the agents are given in a dose range where the biological response is a linear function of dose) or multiplicative (if the response is a simple exponential response to dose), synergistic (greater than expected) or antagonistic (less than expected).

The agency knows of no method where by potential multiplicative, synergistic, or antagonistic interactions can be incorporated into a generalized risk assessment process. Furthrmore. at the dose levels under consideration (far below those having measurable pharmacologic or physiologic activity), the agency sees no reason to consider synergistic or antagonistic interactions. When one extrapolates carcinogenicity data downward to very low doeses, one is, in effect, assuming that the carcinogens are acting independently, and that no interactions occur. Thus, if the probability of developing cancer from one substance is independent of the probability of developing cancer from another substance, then the probability of developing cancer from either substance may be obtained from summing the individual probabilities. Therefore, in the absence of specific information on the interactions among the carcinogenic impurities, the agency believes that, operationally, the risks incurred from the presence of multiple carcinogenic impurities in a color or food additive can be considered independent, and that the estimated upper bound risks should be summed.

The individual risk estimates discussed earlier show that the impurities other than 4-aminobiphenyl and benzidine make negligible contributions to the total risk. Table III shows the total upper bound risk, estimated by summing the risk estimate from each carcinogenic impurity when present at the highest level, consistent with specifications, to be 4 in 100 million.

TABLE III—UPPER BOUND RISK ESTIMATES BASED ON SPECIFICATIONS FOR CARCINOGENIC IMPURITIES IN D&C RED NO. 33

Impurity	Lifetime cancer risk	
4-Aminoazobenzene [1]	0.000000002	($2X10^{-9}$)
4-Aminobiphenyl [1]	0.00000002	($2X10^{-8}$)
Aniline	0.00000000004	($4X10^{-11}$)
Azobenzene	0.00000000002	($2X10^{-11}$)
Benzidine	0.00000002	($2X10^{-8}$)
1,3-Diphenyltriazene [1]	0.00000000001	($1X10^{-11}$)
Sum [2]	0.00000004	($4X10^{-8}$)

[1] The risk for skin cancer is used here because it is higher than the risk estimated for systemic cancer.
[2] In summing risk estimates, numbers have been rounded off to the nearest significant figure.

The agency emphasizes that these upper bound risk estimates are worst case estimates that are used to assure that there is a reasonable certainty that use of an additive will not cause harm. Consequently, several assumptions used for the estimate tend to overestimate rather than underestimate risk. For example, the linear model used to extrapolate risk to low dose exposure is a conservative model. It is used to generate an upper bound estimate of an unknown risk, not to predict an actual risk.

Furthermore, the agency's risk estimates are based on the assumption that all carcinogenic impurities are present at the maximum concentrations allowed by the regulations. In reality, any batch with any impurity concentration above a specification would be rejected while batches with lower concentrations would be allowed. Therefore, unless all batches of certified color additive have impurity concentrations exactly at the specification limits, the average concentration of each impurity will be lower than the maximum allowed.

Finally, the agency points out that the levels of the impurities found in D&C Red No. 33 are so low that under no circumstances could a bioassay detect a carcinogenic effect from these impurities.

The agency has considered the potential presence of these impurities in other color additives as part of this evaluation. D&C Red No. 33, FD&C Yellow No. 5, and FD&C Yellow No. 6 all can contain the same carcinogenic impurities (50 FR 35774 at 35776; September 4, 1985 and 51 FR 41765 at 41774; November 19, 1986). Currently, the agency can estimate risks only for products containing these three color additives with these impurities. Simple addition of the upper bound risks for high users of each color additive (all projected to have the impurities present at the levels of the specifications) would give a value of less than 8 in 10 million. Although this value is clearly exaggerated, FDA sees no need to refine the analysis when the risk is so low.

The agency believes that the maximum risk to consumers from the use of D&C Red No. 33 alone or in combination with the other additives is sufficiently low that it can conclude that the use of batches of D&C Red No. 33 that meet the specifications adopted by this rule is safe. The agency is aware that some of these carcinogenic impurities may occur also in some color additives other than FD&C Yellow No. 5 and FD&C Yellow No. 6. Due to the small amounts of these other color additives that are manufactured, or the limited usage, FDA does not expect any noticeable risk from these sources. The agency will review any risk resulting from exposure to these impurities in other color additives, and will take whatever regulatory action is needed to protect the public health, when sufficient information is available for an appropriate decision.

V. Refrences

The following references have been placed on file at the Dockets Management Branch (address above) and may be seen in that office between 9 a.m. and 4 p.m., Monday through Friday.

1. National Toxicology Program, "Peer Review of the Data from the Chronic Carcinogenesis Animal Bioassay of D&C Red No. 33 by the Technical Reports Review Subcommittee and Panel of Experts," July 26, 1984.

2. Memorandum, McLaughlin, P.J., to File for D&C Red No. 33, "Comparative Evaluation for Additional Safety Considerations, D&C Red No. 33," July 5, 1988.

3. Memorandum, Quantitative Risk Assessment Committee, "Carcinogenicity Risk Analysis for D&C Red No. 33 and D&C Red No. 36, Including a Discussion of ENVIRON/CTFA's Risk Analysis and Incorporation of Recommendations of the Color Additive Scientific Review Panel," March 12, 1987.

4. FDA, Bureau of Foods, "Toxicological Principles for the Safety Assessment of Direct Food Additives and Color Additives Used in Food," 1982.

5. Memorandum, Link, W.B., to E. Coleman, "Amines in D&C Red No. 33," August 12, 1983.

6. Memorandum, Bailey, J.E., to E. Coleman, "1,3-Diphenyltriazene and Azobenzene in D&C Red No. 33," September 19, 1983.

7. Memorandum, Quantitative Risk Assessment Committee, "Upper Bound Risks from Carcinogenic Impurities in D&C Red No. 33 and D&C Red No. 36," March 31, 1987.

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VI. Conclusions

The agency concludes that D&C Red No. 33 is safe under the conditions of use set forth below for general use in drugs and cosmetics, and that certification is necessary for the protection of the public health. In reaching this conclusion, the agency evaluated a full battery of animal feeding and dermal studies adequate to demonstrate the safety of a color additive. The agency also performed a comparative evaluation on the splenic toxicity of D&C Red No. 33 and D&C Red No. 9 to determine whether additional animal safety testing was needed to achieve a reasonable certainty that no harm would result from use of D&C Red No. 33. Based on all the relevant data, including the comparative splenic toxicity evaluation, the agency concludes that there is a reasonable certainty of no harm from use of the additive and that further testing is unnecessary and of no benefit to the public health.

The final toxicity study reports, interim reports, and the agency's evaluations of these studies are on file at the Dockets Management Branch (address above) and may be reviewed there between 9 a.m. and 4 p.m., Monday through Friday.

The agency concludes that it is necessary to have limitations on the levels of D&C Red No. 33 that may be used in drugs and cosmetics to assure safe use.

The petitioners have not submitted the required data for eye-area use. Therefore, FDA now considers that portion of the petition that included the permanent listing of D&C Red No. 33 for eye-area use to be withdrawn without prejudice in accordance with the provisions of § 71.4 (21 CFR 71.4). Use of D&C Red No. 33 in the area of the eye has never been covered by provisional listing. The agencys listing of a color additive for general use in drugs and cosmetics does not encompass eye-area use.

The agency is describing the color additive in this regulation according to the current Chemical Abstracts nomenclature, which differs somewhat from the nomenclature FDA previously used.

The agency concludes that it is necessary to include in the listing regulations for D&C Red No. 33 a brief description of its manufacturing process to ensure the safety of the color additive. FDA has included that description to define as closely as possible the color additive that has been tested and shown to be safe. The agency is doing so because use of a different manufacturing process is likely to produce different impurities that have not been considered in establishing specifications for this color additive. The agency is not able at this time to set specifications that would control the presence of all such impurities. FDA is willing to consider petitions for alternative manufacturing processes, but those petitions should contain evidence that demonstrates that those processes will not produce impurities that will make use of the color additive unsafe.

The agency has contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to develop appropriate specifications for color additives for use in food as part of the Food Chemical Codex. Similarly, appropriate specifications for color additives for use in drugs and cosmetics will be developed following the general guidelines used by NAS/NRC in its evaluation of color additives used in food. The agency concludes that specifying, through a general decription, the manufacturing process in the regulations for this color additive will provide an adequate assurance of safety until suitable specifications can be developed.

The agency finds that because of the presence, or possible presence, of carcinogenic impurities in the color additive, specifications for impurities are necessary to protect the public health. Therefore, specifications as listed in Table II, column 2, of this preamble are included in the regulation.

In the past, D&C lakes have been permitted to be prepared from uncertified straight color additives. The resulting lakes would subsequently be certified. However, to assure that all lakes meet the specification limits for the carcinogenic impurities and that the use of lakes remains consistent with the evaluation, the agency is establishing the requirement that all lakes of D&C Red No. 33 be prepared from certified batches of the straight color additive. Accordingly, § 82.1333 is amended to reflect this requirement.

This order does not permanently list D&C Red No. 33 lakes. FDA published a notice of intent in the **Federal Register** of June 22, 1979 (44 FR 36411), which discussed the additional information that the agency believes is needed before final regulations on lakes can be issued. FDA intends to publish proposed regulations governing the use of color additives in lakes in the **Federal Register** in the near future and concludes that the listing of color additives for use in lakes can best be implemented by general regulations. D&C Red No. 33 lakes will, therefore, continue to be provisionally listed for coloring drugs and cosmetics under Parts 81 and 82 (21 CFR Parts 81 and 82).

The agency has determined under 21 CFR 25.24(b)(3) 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. Objections

Any person who will be adversely affected by this regulation may at any time on or before September 29, 1988, file with the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written objections thereto. Each objection shall be separately numbered, and each numbered objection shall specify with particularity the provisions of the regulation to which objection is made and the grounds for the objection. Each numbered objection on which a hearing is requested shall specifically so state. Failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held. Failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 74

Color additives, Cosmetics, Drugs.

21 CFR Part 81

Color additives, Cosmetics, Drugs.

21 CFR Part 82

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, Parts 74, 81, and 82 are amended as follows:

PART 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. The authority citation for 21 CFR Part 74 continues to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055–1056 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

2. Section 74.1333 is added to Subpart B to read as follows:

§ 74.1333 D&C Red No. 33.

(a) *Identity.* (1) The color additive D&C Red No. 33 is principally the disodium salt of 5-amino-4-hydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid (CAS Reg. No. 3567–66–6). To manufacture the additive, the product obtained from the nitrous acid diazotization of aniline is coupled with 4-hydroxy-5-amino-2,7-naphthalenedisulfonic acid in an alkaline aqueous medium. The color additive is isolated as the sodium salt.

(2) Color additive mixtures for drug use made with D&C Red No. 33 may contain only those diluents that are suitable and that are listed in Part 73 of this chapter as safe for use in color additive mixtures for coloring drugs.

(b) *Specifications.* D&C Red No. 33 shall conform to the following specifications and shall be free from impurities other than those named to the extent that such impurities may be avoided by current good manufacturing practices:

Sum of volatile matter at 135 °C (275 °F) and chlorides and sulfates (calculated as sodium salts), not more than 18 percent.
Water-insoluble matter, not more than 0.3 percent.
4-Amino-5-hydroxy-2,7-naphthalenedisulfonic acid, disodium salt, not more than 0.3 percent.
4,5-Dihydroxy-3-(phenylazo)-2,7-naphthalenedisulfonic acid, disodium salt, not more than 3.0 percent.
Aniline, not more than 25 parts per million.
4-Aminoazobenzene, not more than 100 parts per billion.
1,3-diphenyltriazene, not more than 125 parts per billion.
4-Aminobiphenyl, not more than 275 parts per billion.
Azobenzene, not more than 1 part per million.
Benzidine, not more than 20 parts per billion.
Lead (as Pb), not more than 20 parts per million.
Arsenic (as As), not more than 3 parts per million.
Mercury (as Hg), not more than 1 part per million.
Total color, not less than 82 percent.

(c) *Uses and restrictions.* The color additive D&C Red. No 33 may be safely used for coloring ingested drugs, other than mouthwashes and dentifrices, in amounts not to exceed 0.75 milligram per daily dose of the drug. D&C Red No. 33 may be safely used for coloring externally applied drugs, mouthwashes, and dentifrices in amounts consistent with current good manufacturing practice.

(d) *Labeling requirements.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Red No. 33 shall be certified in accordance with regulations in Part 80 of this chapter.

3. Section 74.2333 is added to Subpart C to read as follows:

§ 74.2333 D&C Red No. 33.

(a) *Identity and specifications.* The color additive D&C Red No. 33 shall conform in identity and specifications to the requirements of § 74.1333(a) (1) and (b).

(b) *Uses and restrictions.* The color additive D&C Red No. 33 may be safely used for coloring cosmetic lip products in amounts not to exceed 3 percent total color by weight of the finished cosmetic products. D&C Red No. 33 may be safely used for coloring mouthwashes (including breath fresheners), dentifrices, and externally applied

cosmetics in amounts consistent with current good manufacturing practice.

(c) *Labeling requirements.* The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of § 70.25 of this chapter.

(d) *Certification.* All batches of D&C Red No. 33 shall be certified in accordance with regulations in Part 80 of this chapter.

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

4. The authority citation for 21 CFR Part 81 continues to read as folows:

Authority: Secs. 701, 706, 52 Stat. 1055–1056 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371, 376); Title II, Pub. L. 86–618, sec. 203, 74 Stat. 404–407 (21 U.S.C. 376, note); 21 CFR 5.10.

§ 81.1 [Amended]

5. Section 81.1 *Provisional lists of color additives* is amended by removing the entry for "D&C Red. No. 33" from the table in paragraph (b).

§ 81.25 [Removed]

6. Section 81.25 *Temporary tolerances* is removed.

§ 81.27 [Amended]

7. Section 81.27 *Conditions of provisional listing* is amended by removing the entry for "D&C Red. No. 33" from the table in the introductory text of paragraph (d).

PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

8. The authority citation for 21 CFR Part 82 continues to read as follows:

Authority: Secs. 701, 706, 52 Stat. 1055–1056 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371, 376); 21 CFR 5.10.

9. Section 82.1333 is revised to read as follows:

§ 82.1333 D&C Red No. 33.

(a) The color additive D&C Red. No. 33 shall conform in identity and specifications to the requirements of § 74.1333(a) (1) and (b) of this chapter.

(b) All lakes of D&C Red. No. 33 shall be manufactured from previously certified batches of the straight color additive.

Dated: August 23, 1988.

John M. Taylor,

Associate Commissioner for Regulatory Affairs.

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21 CFR Part 314

[Docket No. 82N–0293]

Technical Revision in Regulations Governing Drug Master File Submissions

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is making a minor revision of the rules governing the submission to FDA of Drug Master Files (DMF's). DMF's are reference files submitted to FDA generally in support of investigational and marketing applications for human drugs. The final rule reduces from three to two the number of copies of a DMF required to be submitted. This change will eliminate the submission of unneeded material and will reduce the volume of submissions.

DATES: Effective September 29, 1988; comments by October 31, 1988.

ADDRESS: Written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Adele S. Seifried, Center for Drug Evaluation and Research (HFD–362), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8046.

SUPPLEMENTARY INFORMATION: DMF's are reference files submitted to FDA that generally are used in the review of investigational and marketing applications for human drugs. DMF's are often submitted to the agency to allow another party to reference this material without disclosing to that party the contents of the file. In the **Federal Register** of February 22, 1985 (50 FR 7452 at 7493), FDA adopted new regulations governing the submission and content of DMF's. The agency is now making a minor change in these requirements.

The current regulation requires that DMF's be submitted in triplicate (21 CFR 314.420(c)). FDA has found that two copies of the drug master file are adequate and has revised the regulation accordingly.

This revision is consistent with the guidance provided in the "Draft Guideline for Drug Master Files" made available under a notice published in the **Federal Register** of October 15, 1987 (52 FR 38276).

Notice and comment procedure is not necessary before issuing this technical revision (5 U.S.C. 553(b)(B); 21 CFR 10.40(e)(1)). This regulation does not impose any new requirements but merely makes a minor technical revision of the DMF regulations already in place. This revision is intended to assist both DMF submitters and FDA by eliminating submission of an unneeded copy. No useful purpose would be served by notice and comment. The Commissioner has therefore determined for good cause that notice and comment are unnecessary and contrary to the public interest.

This technical revision becomes effective on September 29, 1988. However, interested persons may, on or before October 31, 1988, submit written comments to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Such comments will be considered in determining whether amendments, modifications, or revisions to the final rule are warranted. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Environmental Impact

The agency has determined under 21 CFR 25.24(a)(9) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Economic Impact

In accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354), the agency has carefully analyzed the economic consequences of this final rule. This final rule is merely a technical revision of an existing rule which will have minor but beneficial economic consequences, and the agency has determined that it is, therefore, not a major rule as defined in Executive Order 12291. Further, the Commissioner certifies that this clarification will not have a significant impact on a substantial number of small entities, as defined in the Regulatory Flexibility Act.

Paperwork Reduction Act

The minor technical changes under this rule relate to collection of