Dated: May 6, 1982.

John A. Svahn,

Commissioner of Social Security.

Approved: May 6, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

PART 416—SUPPLEMENTAL SECURITY INCOME FOR THE AGED, BLIND, AND DISABLED

Part 416 of Title 20 of the Code of Federal Regulations is amended as follows:

Subpart K—Income

1. The authority citation for Subpart K of Part 416 reads as follows:

Authority: Secs. 1102, 1611, 1612, 1613, 1614, and 1631 of the Social Security Act as amended; Sec. 211 of Pub. L. 93–66; 49 Stat. 647 as amended, 86 Stat. 1466, 86 Stat. 1468; 86 Stat. 1470, 86 Stat. 1471, 86 Stat. 1475, 87 Stat. 154; 42 U.S.C. 1302, 1382, 1382a, 1382b, 1382c, and 1383.

2. Section 416.1161a is added to read as follows:

§ 416.1161a Income for deeming purposes where Medicaid eligibility is affected.

(a) *General.* In many States, an individual who is eligible for SSI or a Federally administered State optional supplementary payment is in turn eligible for Medicaid. In these States, in extraordinary cases, the Department will not apply the usual rules on deeming of income where those rules would result in an individual's being ineligible for SSI (or a Federally administered State optional supplementary payment) and Medicaid. Any determination made under this section may at any time be revised based on new information or changed circumstances.

(b) *When special deeming rules apply.* (1) The Department will consider not applying the usual deeming rules only upon application by a State Medicaid agency (requirement approved under OMB No. 09600304) and on condition that the agency must show:

(i) Deeming would result in lack of Medicaid eligibility for the individual

(ii) Medicaid eligibility would, prospectively, result in savings to the Medicaid program; and

(iii) The quality of medical care necessary for the individual would be maintained under the arrangements contemplated.

(2) The Department may also in particular cases require that additional facts be demonstrated, or that other criteria or standards be met, before it determines not to apply the usual deeming rules.

(c) *Amount of income to be deemed.* If the usual rules of deeming do not apply, the Department will determine an amount, if any, to be deemed.

(d) *Temporary effect of special deeming rules.* This provision is temporary and will be continued only through April 30, 1983, unless extended. Determinations made under this section will nevertheless remain in effect unless they are revised based on changed circumstances (including establishment in the State of a Medicaid program of home and community-based services) or new information.

Subpart L—Resources and Exclusions

3. The authority citation for Subpart L of Part 416 reads as follows:

Authority: Secs. 1102, 1601, 1602, 1611, 1612, 1613, 1614(f), and 1631(d), of the Social Security Act, as amended, 49 Stat. 647 as amended, 86 Stat. 1465, 1466, 1468, 1470, and 1473; 42 U.S.C. 1302, 1381, 1381a, 1382, 1382a, 1382b, 1382c(f), and 1383(d), unless otherwise noted.

4. Section 416.1204a is added to read as follows:

§ 416.1204a Deeming or resources where Medicaid eligibility is affected.

Section 416.1161a of this part describes certain circumstances affecting Medicaid eligibility in which the Department will not deem family income to an individual. The Department will follow the same standards, procedures, and limitations set forth in that section with respect to deeming of resources.

[FR Doc. 82–15102 Filed 6–3–82; 8:45 am]

BILLING CODE 4190–11–M

Food and Drug Administration

21 CFR Part 20

[Docket No. 81N–0043]

Freedom of Information Files

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the FDA regulation on record retention of files on freedom of information requests. The amendment will allow for a reasonable record retention and destruction plan and relieve FDA of the burden of keeping these files indefinitely.

EFFECTIVE DATE: June 4, 1982.

FOR FURTHER INFORMATION CONTACT: Gerald Deighton, Freedom of Information Staff (HFI–30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1813.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 162), FDA published a proposal to amend the FDA regulation on record retention of files on freedom of information requests. The proposal allowed for the filing of comments by March 8, 1982.

Two comments were received. One comment, from the Acting Assistant Archivist for Federal Records Centers, General Services Administration (GSA), stated that the GSA General Records Schedule (GRS) 14 is mandatory and any deviation from the GRS standards that FDA might wish to make on the basis of comments received on the proposal must be approved by the archivist of the United States.

The amendments set forth in the January 5, 1982 proposal and as adopted below bring FDA's regulation into conformance with the GRS standards.

The other comment, from an individual, supported the proposal, but stated that the regulation should be simpler, shorter, and clearer.

The agency has carefully considered the comment, but has concluded that the amendments should be adopted as proposed.

List of Subjects in 21 CFR Part 20

Freedom of information.

PART 20—PUBLIC INFORMATION

Accordingly, under the Federal Food, Drug, and Cosmetic Act (sec. 701(a), 52 Stat. 1055 (21 U.S.C. 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Part 20 is amended by revising § 20.31, to read as follows:

§ 20.31 Retention schedule of requests for Food and Drug Administration records.

(a) Unless unusual circumstances dictate otherwise, the Food and Drug Administration shall maintain and dispose of files of requests and reponses furnished thereto within the time limits authorized by GSA General Records Schedule 14, FPMR 101–11–4, January 10, 1977, as follows:

(1) Files created by the receipt of and response to freedom of information requests, except denials and/or appeals, may be destroyed 2 years from date of final response.

(2) Files created by a freedom of information request which was wholly or partially denied may be destroyed 5 years after the denial letter was issued.

(3) Files created by a freedom of information request which was wholly or partially denied and which denial

was subsequently appealed to the Department of Health and Human Services may be destroyed 4 years after final determination by FDA or 3 years after final adjudication by courts, whichever is later.

(b) This destruction schedule will automatically be revised whenever the time limits pertaining to these records are revised by the GSA General Records Schedule.

Effective date. June 4, 1982.

(Sec. 701(a), 52 Stat. 1055 (21 U.S.C. 371(a)))

Dated: May 28, 1982.

Joseph P. Hile,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 82-15129 Filed 6-3-82; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Parts 74, 81, and 82

[Docket No. 81N-0301]

D&C Green No. 6; Listing as a Color Additive in Externally Applied Drugs and Cosmetics; Confirmation of Effective Date

AGENCY: Food and Drug Administration.

ACTION: Final rule; confirmation of effective date.

SUMMARY: The Food and Drug Administration (FDA) is confirming the effective date of May 4, 1982, for a final rule that amended the color additive regulations by "permanently" listing D&C Green No. 6 for use in externally applied drugs and cosmetics. That document also provided for the depletion of existing stocks of D&C Green No. 6 for all uses involving ingestion of the color additive.

DATE: Effective date confirmed: May 4, 1982.

FOR FURTHER INFORMATION CONTACT: Garnett R. Higginbotham, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

SUPPLEMENTARY INFORMATION: FDA published a final rule in the **Federal Register** of April 2, 1982 (47 FR 14138) that amended the color additive regulations by "permanently" listing D&C Green No. 6 for use in externally applied drugs and cosmetics. That document also provided for the depletion of existing stocks of D&C Green No. 6 for all uses involving ingestion of the color additive.

Interested persons were given until May 3, 1982, to file objections. FDA received no objections on the final rule. Therefore, the agency concludes that the final rule published on April 2, 1982, for D&C Green No. 6 should be confirmed.

List of Subjects in 21 CFR Parts 74, 81, 82

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 701, 706, 52 Stat. 1055-1056 as amended, 74 Stat. 399-407 as amended (21 U.S.C. 371, 376)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), notice is given that no objections or requests for a hearing were filed in response to the final rule of April 2, 1982. Accordingly, the amendments promulgated thereby became effective on May 4, 1982.

Dated: May 27, 1982.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 82-14964 Filed 5-28-82; 11:30 am]

BILLING CODE 4160-01-M

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21 CFR Parts 74, 81, and 82

[Docket No. 76C-0045]

D&C Green No. 5

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is "permanently" listing D&C Green No. 5 for use in drugs and cosmetics excluding use in the area of the eye. This action is in response to a petition filed by the Cosmetic, Toiletry, and Fragrance Association, Inc., the Pharmaceutical Manufacturers Association, and the Certified Color Manufacturers Association, Inc. This rule will remove D&C Green No. 5 from the provisional list of color additives for use in drugs and cosmetics.

DATES: Effective July 7, 1982; objections by July 6, 1982.

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: For general information: Rudolph Harris, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

For information relating to the safety evaluation of D&C Green No. 5: Terry C. Troxell, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5690.

SUPPLEMENTARY INFORMATION:

I. Introduction

The Color Additive Amendments of 1960 (the amendments) require FDA Premarket clearance of any color additive that is intended to be used or that is represented for use in or on food, drugs, certain medical devices, cosmetics, or the human body. Under the amendments, a use of a color additive may be approved and listed if there are sufficient data establishing that the color additive is safe for its intended use.

Recognizing that many colors were already in use at the time it enacted the amendments, Congress established transitional provisions to allow for the provisional listing and continued use of color additives for a period of time necessary to complete scientific investigations needed to evaluate their safety under the standards prescribed in the amendments.

Section 81.1 of the color additive regulations (21 CFR 81.1) identifies those color additives that are provisionally listed under section 203(b) of the Transitional Provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86-618), sec. 203, 74 Stat. 404-407 (21 U.S.C. 376, note)) and sets forth the closing date for each color additive. A closing date is the last day upon which a provisionally listed color additive can be used legally, absent an approval of a color additive petition and its listing. (See section 203(a)(1) of the Transitional Provisions.)

The color additive D&C Green No. 5 has been provisionally listed for use in ingested and externally applied drugs and cosmetics since the enactment of the amendments. During that time, a series of toxicological studies have been performed on this color additive. Based upon the evaluation of the results of these studies and other pertinent data, the agency concluded that D&C Green No. 5 is safe for use in ingested and externally applied drugs and cosmetics. FDA is therefore listing D&C Green No. 5 for such uses.

II. Regulatory History of D&C Green No. 5

D&C Green No. 5 was provisionally listed as a color additive for use in drugs and cosmetics in 1960 (25 FR 9759; October 12, 1960).

FDA published a notice in the **Federal Register** of November 20, 1968 (33 FR 17205) that a petition (CAP 8C0084) for the listing of D&C Green No. 5 as a color additive for use in drugs and cosmetics had been filed by the Toilet Goods Association, Inc. (now the Cosmetic, Toiletry, and Fragrance Association, Inc. (CTFA)); the Pharmaceutical Manufacturers Association (PMA); and the Certified Color Industry Committee (now the Certified Color Manufacturers

Association, Inc.), c/o Hazelton Laboratories, Inc., 9200 Leesburg Turnpike, Vienna, VA 22180. The petition was filed pursuant to section 706 of the act (21 U.S.C. 376). A subsequent notice published in the Federal Register of March 5, 1976 (41 FR 9584) amended the notice of filing for this petition to include the additional use of D&C Green No. 5 in cosmetics intended for use in the area of the eye. This latter use is not addressed in this final regulation but will be the subject of a later agency decision following receipt of appropriate data on this use.

Regulations published in the Federal Register of February 4, 1977 (42 FR 6991), required new chronic toxicity studies for D&C Green No. 5 as a condition of its continued provisional listing for ingested uses. Additional studies were not required for use of this color additive in externally applied drugs and cosmetics. The closing date for the provisional listing of the color additive for both ingested and external uses was postponed until January 31, 1981, for completion of the studies. Although the agency had intended to issue a rule on D&C Green No. 5 before expiration of the January 31, 1981 closing date, the order did not publish before President Reagan signed his Executive Memorandum of January 29, 1981, which directed agencies to postpone for 60 days all pending regulations, with certain exemptions that were inapplicable to the D&C Green No. 5 rule. The rule was published as soon as possible after the end of the postponement, in the Federal Register of March 27, 1981 (46 FR 18958). In that rule the agency established a new closing date of May 30, 1982, for the completion of the chronic toxicity studies and the submission of data to FDA on a prescribed schedule. The provisional listing in § 81.1(b) of D&C Green No. 5 will be removed when this order becomes effective on July 7, 1982, unless this order is stayed by the timely filing of objections. Published elsewhere in this issue of the Federal Register is an order extending the closing date for D&C Green No. 5 until August 3, 1982, to provide time for the submission and receipt of objections.

D&C Green No. 5 is currently listed as a color additive in nylon 66 and nylon 6 nonabsorbable surgical sutures (21 CFR 74.1205). The specifications published in this regulation for ingested and externally applied D&C Green No. 5 differ from those currently established for D&C Green No. 5 for use in coloring sutures. FDA is listing the color additive with two sets of specifications and will propose in the near future to remove the specifications for D&C Green No. 5 for use in coloring sutures. At the present time either set of specifications may be used for sutures.

III. Description of D&C Green No. 5

D&C Green No. 5 is principally the disodium salt of 2,2'-((9,10-dihydro-9,10-dioxo-1,4-anthracenediyl)diimino)bis-(5-methylbenzesulfonic acid) (CAS Reg. No. 4403–90–1). The manufacture of D&C Green No. 5 is accomplished by the sulfonation of D&C Green No. 6 with fuming sulfuric acid. Because D&C Green No. 6 is the starting material in this manufacturing process, the possibility exists that the chemicals used in the synthesis of D&C Green No. 6 may be present in minor amounts in D&C Green No. 5. In the preamble of the April 2, 1982 final regulation permanently listing D&C Green No. 6 (47 FR 14138), FDA explained that D&C Green No. 6 is formed by chemically reacting one molecule of quinizarin with two molecules of *p*-toluidine. The significance of these components is that Weisburger, et al., have demonstrated that *p*-toluidine is a carcinogen in mice.[1]

Residual amounts of reactants, such as *p*-toluidine and related manufacturing aids, are commonly found among the constituents of many color additives. The presence of such constituents is not unique to color additives, however. Numerous contaminants are unavoidably present in all chemical products, even in highly purified reagent grade chemicals.

Until recently there was no analytical evidence that *p*-toluidine actually is present in D&C Green No. 5. FDA did not detect *p*-toluidine in D&C Green No. 5 using a gravity elution chromatography method, an analytical procedure for uncombined intermediates. FDA considers the sensitivity of this method for *p*-toluidine to be at least 250 ppm. Because of the concern about the carcinogenic potential of *p*-toluidine, the agency asked CTFA to develop an analytical method that would reliably measure *p*-toluidine in D&C Green No. 5.

In response to the FDA's request, CTFA submitted a report prepared by Shiseido Laboratories (Yokohama, Japan) on the determination of residual *p*-toluidine in D&C Green No. 5. Shiseido's method uses high performance liquid chromatography (HPLC) separation with fluorescence detection. The reported limit of detection for this method is 0.1 ppm. Reproducibility and recovery data that were provided for a D&C Green No. 5 sample spiked with 3 ppm of *p*-toluidine were very good. FDA considers this method to be a valid analytical method for the determination of residual *p*-toluidine levels in D&C Green No. 5 at least to 3 ppm and probably lower. In addition, a HPLC method for detecting *p*-toluidine with a sensitivity of less than 10 ppm has been developed at FDA.

Using the HPLC method, Shiseido analyzed the residual *p*-toluidine in three commerical samples of D&C Green No. 5 manufactured in the U.S. The *p*-toluidine levels reported by Shiseido for these samples were 0.57, 1.49, and 2.54 ppm. FDA has examined seven additional batches of D&C Green No. 5. The largest response the agency observed was an apparent 2.5 ppm. Based on these analytical results, FDA expects that the average *p*-toluidine level in certified D&C Green No. 5 prepared in accordance with current good manufacturing practice will not exceed 5 ppm.

The *p*-toluidine found in D&C Green No. 5 is utilized in the first step in the synthesis process, the preparation of D&C Green No. 6, and is substantially removed by subsequent reaction with fuming sulfuric acid and purification.

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[1] In a 1978 paper, Weisburger, et al., Journal of Environmental Pathology and Toxicology, 2:325 (1978), reported on the chronic bioassay testing of *p*-toluidine, among 20 other aromatic amines and related compounds, for potential carcinogenicity. These studies were conducted under contract from the National Cancer Institute. *p*-Toluidine was orally administered to male Charles River CD (Sprague-Dawley derived) rats and to male and female Charles River CD–1 (HaM/ICR derived) mice (25 animals/sex/dose). The treatment levels employed were the maximum tolerated dose (MTD) and ½ MTD and were administered for 18 months followed by either a 3-month (mice) or 6-month (rats) delay in terminal sacrifice to allow time for expression of latent tumors. The dietary treatment levels were: 1. Rats—MTD = 2,000 ppm (parts per million), ½ MTD = 1,000 ppm and; 2. Mice—MTD = 2,000 ppm for 6 months and 1,000 ppm for the next 12 months, ½ MTD = 1,000 ppm for 6 months and 500 ppm for the next 12 months. The treated rats showed no increase in the incidence of tumors at any site examined. Male mice at both dose levels exhibited a statistically significant increase in hepatomas (liver tumors) as compared to untreated control groups. Female mice at the high dose level (MTD) showed a marginally significant increase of hepatomas. Male mice showed a much greater sensitivity to hepatoma induction than female mice.

Based on the conditions and results of this study, *p*-toluidine can be considered to be an animal carcinogen. Compared to other known animal carcinogens, its potency for inducing tumors is relatively weak, as shown by high dose levels required to induce tumors, and by the fact that tumor incidence was greatly enhanced in only 1 tissue type in 1 of the 3 sex/species groups tested.

The Cancer Assessment Committee of FDA's Bureau of Foods reviewed this study and other relevant data available in the literature pertaining to the potential carcinogenicity of *p*-toluidine. The Committee concluded "that the oral administration of *p*-toluidine induces liver tumors in male and, perhaps, female mice." The Committee further concluded that an estimate of the upper limit of human cancer risk from exposure to *p*-toluidine can be made based on the Weisburger, et al., study.

Residual *p*-toluidine is not intended to and does not contribute any color to D&C Green No. 5, nor does it impart any color to drugs, cosmetic, or the human body. Consequently, FDA concludes that, although a small amount of *p*-toluidine is added to drugs and cosmetics with the addition of D&C Green No. 5, this chemical is not a color additive within the meaning of 21 U.S.C. 321(t) but is merely an impurity in D&C Green No. 5.

IV. Evaluation Of The Safety Of D&C Green No. 5 For Drugs And Cosmetic Use

A. *Statutory Safety Requirements.* Under section 706(b)(4) of the Federal Food, Drug, and Cosmetic Act (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 the color 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. Rep. 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 establishes that Congress did not intend the term "safe" to require absolute proof of safety. The Senate report 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 circumstance.
>
> 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. Rep. No. 2422, "Food Additive 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 (21 U.S.C. 376(b)(5)(B)), which provides that a color additive like D&C Green No. 5 shall be deemed to be unsafe "if, the additive is found by the Secretary to induce cancer when ingested by man or animal" (21 U.S.C. 376(b)(5)(B)(i)).

B. *Prior Action by FDA.* In the past, FDA has terminated the provisional listing of several color additives that contained or were expected to contain a carcinogenic impurity or constituent. FDA terminated the provisional listing of carbon black (41 FR 41857; September 23, 1976) and graphite (42 FR 60734; November 29, 1977) because the agency expected that these colors contained polynuclear aromatic hydrocarbons (PNA's). The agency removed Ext. D&C Yellow No. 1 (42 FR 62478; December 13, 1977) from the provisional list because of evidence that this color could contain low levels of 4-aminobiphenyl and benzidine as impurities, and it terminated the listing of D&C Red Nos. 10, 11, 12, and 13 (42 FR 62475; December 13, 1977) because of the possibility that they contain -naphthylamine. In each of these actions, FDA was unable to resolve questions about the safety of use of these additives that were created by the presence of the carcinogenic impurity or constituent. Consequently, the agency acted under section 203(d)(1)(E) of the Transitional Provisions to remove the colors from the provisional list.[2]

However, FDA no longer believes that it must refuse to list a color additive simply because it contains or is expected to contain a carcinogenic constituent or impurity. This conclusion is supported by the 1979 decision by the United States Court of Appeals for the District of Columbia Circuit in *Monsanto v. Kennedy* 613 F.2d 947 (D.C. Cir. 1979). In discussing whether a substance that migrates into food is a food additive, that court endorsed the concept that there is "administrative discretion, inherent in the statutory scheme, to deal appropriately with de minimis situations." (*Id.* at 955.) The court's holding that FDA has discretion to find that low-level migration into food of substances in indirect additives is so insignificant as to present no public health or safety concern supports the agency's conclusion that, in appropriate circumstances, it can make a similar finding about a carcinogenic constituent or impurity that is present in a color additive.

In addition, the agency is confident that it possesses the capacity, through the use of extrapolation procedures, to assess adequately the upper limit of risk presented by use of a color additive that contains a carcinogenic impurity but that, in appropriate testing, has not been shown to cause cancer.

Theoretical extrapolation procedures for assessing the risk of low exposure to carcinogenic materials have been discussed for many years. However, FDA has been reluctant to use these procedures for regulatory decisionmaking. Many theoretical models have been developed to extrapolate from animal experimental data to the relatively low levels of possible human exposure at which possible carcinogenic effects cannot be experimentally demonstrated. Although most risk assessment models have their roots to some degree in the biological mechanisms of carcinogenesis (the processes of which still are not well understood), they can vary widely in the risk values that they predict. Thus, knowledge of the true risk at relatively low exposure is elusive.

Nevertheless, even though there is an inadequate scientific basis to have confidence in the accuracy of predictions of actual risk by these procedures, there has been growing recognition in FDA that by using certain conservative extrapolation models, it is possible to estimate an upper limit of risk. (See e.g., "Chemical Compounds in Food-Producing Animals" (44 FR 17069; March 20, 1979) and FDA's decision on lead acetate (45 FR 72112; October 31, 1980, and 46 FR 15500; March 6, 1981).) The estimate of the risk may be exaggerated by these models. However, for this reason, the estimate can be used with confidence to conclude that a substance is safe under specific conditions of use.

Recently, the agency has examined the risk associated with external drug and cosmetic use of D&C Green No. 6 that contains minor amounts of *p*-toluidine (47 FR 14138; April 2, 1981). Based on the estimate of risk, the agency concluded that the exposure to the residual impurity *p*-toluidine from use of drugs and cosmetics containing D&C Green No. 6 was sufficiently low to be considered safe.

Relying on these developments, FDA has proceeded to evaluate the safety of D&C Green No. 5.

C. *Use of D&C Green No. 5.* D&C Green No. 5 is a water soluble, oil insoluble color additive, the primary use

[2] However, FDA has always established specifications for commonly occurring impurities such as lead and arsenic, which are known carcinogens.

of which is in externally applied cosmetics, with minor use in ingested drugs (known use is approximately 100 pounds per year) and apparently trivial use in ingested cosmetics. D&C Green No. 5, a certifiable color, had an average yearly certified poundage of 6,711 pounds between 1970 and 1981. During that period, no lakes of D&C Green No. 5 were certified.

Many cosmetic manufacturers submit Cosmetic Product Ingredient Statements (formulations) to the FDA under the Voluntary Cosmetic Regulatory Program (21 CFR 720). This program provides information on the specific types of cosmetic products in which D&C Green No. 5 is used. Additionally, CTFA has provided data on maximum use levels in cosmetics based on a 1981 survey of manufacturers.

As of December, 1981, FDA's Voluntary Cosmetic Regulatory Program computer file contained 311 formulations that listed D&C Green No. 5 as an ingredient. Of these, 28 percent were noncoloring hair preparations (primarily shampoos and conditioners); 22 percent were fragrance preparations (e.g., colognes and perfumes); 21 percent were skin care preparations (e.g., creams and lotions); and, 12.5 percent were shaving preparations (primarily aftershave lotion). Based on the color intensity (absorptivity) of D&C Green No. 5, a fairly strong coloring effect would be obtained at 100 ppm in typical transparent cosmetic products. This is consistent with CTFA's 1981 survey where they reported that the maximum level of use of D&C Green No. 5 is less than 100 ppm in most products.

The use of D&C Green No. 5 in ingested cosmetics over the past 10 years was reported only in the category mouthwashes/breath fresheners (2 formulations in FDA's computer file) representing only 0.64 percent of total reported formulations. The 1981 CTFA survey indicated that there were no ingested cosmetic products, including lipsticks, that used D&C Green No. 5.

D&C Green No. 5 is used in coloring ingested drugs. The data in the original food additive petition (1968) indicated that D&C Green No. 5 was used to color 22 pharmaceutical products, including 21 for ingested use. Data from a 1976 PMA survey indicated that usage of D&C Green No. 5 had dropped to 14 ingested drugs. The drugs included three over-the-counter (OTC) preparations and seven drugs for long-term use (over 6 weeks), including one long-term pediatric drug. Of the 1,354 pounds of D&C Green No. 5 reported as used in these preparations, 1,250 pounds was used in one elixir product, which has since been discontinued. The daily dose of D&C Green No. 5 in current known drug products varies from 0.012 milligram per day to 2.28 miligrams per day.

Although the fraction of D&C Green No. 5 used in ingested drugs apparently is minor at this time, use in ingested drugs as provided in this rule represents the greatest potential internal exposure for individuals to this color additive. FDA estimates that D&C Green No. 5 may be used in a particular drug at a maximum level that could result in consumption of 50 mg per day of the color additive. However, the agency believes that lifetime averaged exposure from use of drugs containing D&C Green No. 5 would be a small fraction of the maximum exposure that might occur in a day. As a result, considering probable drug use and all other probable applications in compliance with these regulations, the lifetime-averaged individual exposure (internal and external) to D&C Green No. 5 is not likely to exceed 10 mg per day. Lifetime-averaged individual internal exposure, based on all known uses, would not likely exceed several tenths of a mg per day.

D. *Safety Studies on D&C Green No. 5.* To establish that D&C Green No. 5 is safe for use in ingested and externally applied drugs and cosmetics, the petitioners submitted reports on a number of animal toxicology studies on D&C Green No. 5. Among these studies were a lifetime oral feeding study in rats, a 2-year feeding study in dogs, and a three generation reproduction study in rats. There were no significant compound-related adverse effects observed in these studies.

FDA, however, concluded that the sensitivity (or power) of these chronic feeding toxicity studies was insufficient under current standards to provide the requisite demonstration of safety for ingested use. As a result, CTFA sponsored additional chronic feeding studies on D&C Green No. 5. The studies were conducted by Hazleton Laboratories America, Inc., Vienna, VA, and included a long-term feeding study on D&C Green No. 5 in rats exposed in utero and a long-term feeding study in mice. On May 29, 1981, the agency received the final reports on these studies from CTFA.

In the CTFA-sponsored studies in rats, D&C Green No. 5 was fed to Sprague-Dawley CD–1 rats exposed in utero at dietary levels of 0, 0.10, 0.25, and 1.0 percent for 130 weeks. Seventy males and seventy females were used for each dietary level. The agency concluded that the data from the in utero phase did not reveal any treatment-related differences in the reproduction indices of the treated groups when compared to the controls. The data in the study did indicate that body weight gains were lower in all treated animals during the gestation and lactation period when compared to the controls. In the long-term study there were increases in testicular weight and tests/body ratios. However, there were no reported histological alterations in the testes that could be attributed to treatment. There were no compound-related effects on survival or clinical signs, and no evidence of carcinogenicity in Sprague-Dawley rats.

In the long-term mouse study, D&C Green No. 5 was fed to albino mice (HaM/ICR Swiss) at dietary levels of 0.0, 0.05, 0.50, and 2.0 percent for 88 weeks in males and 97 weeks in females. Sixty males and sixty females were used for each dietary level and in each of two control groups. The toxicological findings in the female mice fed D&C Green No. 5 were comparable to the control group. There were no gross or histopathological changes that could be considered to be treatment related.

In male mice there were more liver neoplasms (hepatocellular adenomas and hepatocellular carcinomas) in the high dose group than in the controls, while their survival was less than that of other dose groups. The number of liver neoplasms in the low dose group was less than the controls, and the number in the intermediate dose group was similar to the controls. The findings were confounded, however, because following the test protocol, only the livers of mice in the control and high dose groups were subject to complete histopathological examination. Those in the low- and mid-dose groups that were grossly normal were not subjected to histopathological examination. The testing laboratory, on the basis of pairwise comparisons between the high dose group and the control groups, using a Fisher's exact statistical test, concluded that there was no significant evidence of a compound-related increase in liver neoplasms, and therefore that there was no need to look at other dosage groups. However, the agency concluded, on the basis of the data initially submitted, and on the assumption that all male mice liver neoplasms had been identified, that early mortality in the high dose group indicated the need for a survival adjusted statistical analysis. The incidental death survival adjusted analysis gave a p-value that was considered statistically significant for combined carcinomas and adenomas.

However, several factors that can be termed "biological" caused the agency to question whether the results of the

statistical analysis established that D&C Green No. 5 is a carcinogen. Historical data document that many strains of mice display a fairly high and variable incidence of spontaneous hepatocellular neoplasms. The agency believed that the incidence of neoplasms found in the high dose group could be within the range of historical spontaneous incidence of hepatocellular neoplasms in this strain of mice for this laboratory. Also, there was no evidence of metastatic disease in any of the treated groups. The presence of this disease might have supported a conclusion that the neoplasms were treatment related. Further, the proportion of livers judged to be normal by gross pathology was virtually identical in treated and control groups. In order to observe more carefully and in greater depth the condition of these livers, FDA requested additional microslides of the livers from male mice in the low- and mid-dose groups, along with the existing slides, for review by agency pathologists, as well as historical data on the incidence of spontaneous hepatocellular neoplasms.

Because of the apparent disparate conclusions the agency reached when it considered biological as opposed to mathematical factors, FDA arranged for external review of the data by the Board of Scientific Counselors (the Board) of the National Toxicology Program (NTP). A notice published in the **Federal Register** of February 19, 1982 (47 FR 7500) announced that the Board would meet to review these data on March 9, 1982 in Conference Rm. 425–403A, Hubert H. Humphrey Bldg., Department of Health and Human Services, 330 Independence Ave. SW., Washington, DC. The Board included the following members:

Dr. Norman Breslow, Department of Biostatistics SC–32, University of Washington, Seattle, WA 98195

Dr. Margaret Hitchcock, Associate Fellow, John B. Pierce Foundation Laboratories, New Haven, CT 06519

Dr. Marjorie G. Horning, Professor of Biochemistry, Institute for Lipid Research, Texas Medical Center, Houston, TX 77030

Dr. Mortimer L. Mendelsohn, Associate Director, Biomedical and Environmental, Lawrence Livermore Laboratory, University of California, Livermore, CA 95550

Dr. Norton Nelson, Director, Institute of Environmental Medicine, New York University Medical Center, 550 First Ave., New York, NY 10016

Dr. Stan D. Vesselinovitch, Professor, Department of Radiology and Pathology, University of Chicago, Chicago, IL 60637

Dr. Alice S. Whittemore, Adjunct Professor, Department of Family Community, and Preventive Medicine, School of Medicine, Stanford University, Stanford, CA 94305.

After considering the data, the Board concluded that the data are "indirect" and "equivocal," and that the statistical evidence is only "limited or suggestive" for carcinogenicity, in spite of the relatively low *p*-values obtained using the trend analysis.

From the data presented to them, the members of the Board could not unequivocally conclude that D&C Green No. 5 was not carcinogenic under the conditions of the test. However, the NTP summary minutes of the Board's meeting indicates that the members of the Board leaned strongly toward such a conclusion. The minutes report that Dr. Mendelsohn stated that "* * * when one considers the lack of toxicity in all the species and sexes looked at, he had to be skeptical as to whether the findings in male mice were significant. He said, at best, the effects were equivocal. Dr. Vesselinovitch agreed and reiterated his views as to the lack of biological significance to the findings."

Dr. Breslow indicated that in his opinion "* * * the most important caveat (to the statistically significant dose-related trend) was that these results take no account of the likely presence of extraneous sources of variation * * *." Based upon his assessment, Dr. Breslow suggested that the agency perform an analysis of variance on the spontaneous incidence of liver neoplasms in male mice of the CD–1 strain at Hazelton Laboratories and in the other studies on color additives currently on the provisional list. The purpose of this analysis would be to determine whether the incidence of hepatocellular tumors in the high dose male group treated with D&C Green No. 5 was significantly higher than the spontaneous background incidence.

FDA conducted the analysis of variance suggested by Dr. Breslow. This analysis indicated that the incidence of liver neoplasms in the high dose male mouse group is not outside the normal range of background spontaneous incidence observed in the historical controls (as defined by two standard deviations).

Traditionally, biologists have considered differences in animal response that are within two standard deviations from the normal variation observed to be of no biological significance. This result of the analysis of variance, therefore, serves to mitigate the significance of the low *p*-values that were calculated based on the use of only the concurrent control groups of animals.

As the agency prepared for the meeting of the Board and in the days following that meeting, as it considered further the results of its analysis of the microslides of the mouse livers, FDA became convinced that the data from the studies were not consistent with the data that would be produced by a carcinogen. The course of hepatocellular neoplastic disease in mice is progressive and is characterized by lesions with different identifiable morphologies and various degrees of size and malignancy. In ascending order, the progression of lesions are: foci of cellular alteration, adenoma, carcinoma, and metastatic carcinoma. A treatment-related production of liver neoplasia can be established not only by an increase in tumor incidence but also by a demonstration that the disease progressed further towards malignancy in treated groups than in the control groups.

The progress of liver cancer can be monitored by comparing the proportion of progressive lesions found in the treated group to that found in the control group. This comparison is actually an indirect measurement of the latency period of carcinogenesis. A shortening of this period is considered to be one of the primary indicators of an induced carcinogenic event, and studies with many bona fide carcinogens have indicated a more dramatic relationship between latency period and treatment than between tumor incidence and treatment.

In the test of D&C Green No. 5, the extent of liver involvement, as measured by the size and type of liver neoplasms, was similar in the treated and control groups. This result suggested to FDA that the small increased incidence of liver tumors in the high dose group was a spurious and nonreproducible occurrence.

In addition, none of the evidence available to the agency provided any basis upon which to expect that the liver is in any way a target organ for D&C Green No. 5. No non-neoplastic pathological changes in the liver were observed, and no enlargement or organ weight differences were noticed. In short, other than the observed higher incidence of liver tumors, there were no indications from pathology observations that the liver was a target organ.

Furthermore, D&C Green No. 5 itself is not mutagenic to several tester strains of *S. typhimurium* with or without activation with liver homogenates.

Finally, even though the trend test produced statistical "significance" for

the male mouse liver data, the apparent dose-response is unlike any observed for compound induced liver neoplasia in the National Cancer Institute (NCI) sponsored bioassay program. If a dose-response curve is constructed using the data, the slope of the curve is much shallower than that observed for chemicals shown to induce carcinogenic effects in the NCI bioassays. This curve does not reflect what the agency considers to be a biologically valid dose-response.

Therefore, collectively there exists a significant body of "biological" evidence that strongly supports the conclusion that D&C Green No. 5 is not a carcinogen. FDA finds that this evidence, when considered in conjunction with the results of the analysis of variance conducted by the agency, refutes any inference from the low *p*-values found in the statistical analysis of the data on D&C Green No. 5 that this color additive is a carcinogen.

Thus, in acceptable carcinogenicity bioassays in two species where numerous tissues were examined in both sexes, a slightly higher number of neoplasms was observed in only one site (the liver), one dose group of one sex and in one species. While two statistical measures (dose-related trend test and pairwise comparison) commonly used in the evaluation of bioassays indicated that this slightly higher number of liver tumors in the high dose group of male mice was statistically significant, all other evidence indicates that the effect was unlikely to be related to treatment with D&C Green No. 5. Evidence supporting the noncarcinogenicity of D&C Green No. 5 includes: (1) the fact that the incidence in the high dose group is within the normal range of background spontaneous incidence; (2) the absence of evidence of progressiveness that would be expected from a carcinogen; (3) the absence of observable non-neoplastic disease in the mouse liver; (4) the negative findings on testing D&C Green No. 5 for mutagenic activity; and (5) the atypical form of the apparent dose-response data. In conclusion, the evidence as a whole, convinces the agency that D&C Green No. 5 is noncarcinogenic (and nontumorigenic) under the conditions of the tests.

E. *Application of risk assessment in this rulemaking.* Because *p*-toluidine is present in D&C Green No. 5 in minor amounts, use of D&C Green No. 5 as authorized by this regulation will likely result in exposure to very small amounts of *p*-toluidine. In determining whether a color additive can be regulated, the terms of the Delaney Clause and the general safety clause must be addressed.

The Delaney Clause requires the disapproval of any color additive that has been shown to be a carcinogen in appropriate testing. However, the agency has concluded that the Delaney Clause applies only when the color additive as a whole is found to cause cancer and does not apply to individual impurity constituents of the color additive. As stated above, the agency finds no basis for concluding that D&C Green No. 5 itself is a carcinogen. The inapplicability of the Delaney Clause in a similar case, D&C Green No. 6, was discussed in the **Federal Register** of April 2, 1982 (47 FR 14138).

FDA does not suggest, however, that the presence of *p*-toluidine in D&C Green No. 5 should be ignored. On the contrary, it should be evaluated under the general safety standards of section 706 of the act, which require that the data establish that the color additive is safe for the regulated use, i.e., there is a reasonable certainty of no harm from the use of the color additive.

As in the D&C Green No. 6 rulemaking, the agency concludes that risk assessment procedures are appropriate to provide a basis for deciding whether there is a reasonable certainty of no harm from the use of D&C Green No. 5 in ingested and externally applied drugs and cosmetics.

The risk evaluation of *p*-toluidine consists of two parts: (a) assessment of probable exposure to *p*-toluidine from use of D&C Green No. 5 in ingested and externally applied drugs and cosmetics, and (b) extrapolation of the risk from *p*-toluidine observed in the animal bioassay to the conditions of probable exposure for humans.

1. *Exposure to p-toluidine.* Two measures of exposure to carcinogenic compounds that are relevant in assessing the public health hazard presented by *p*-toluidine are the maximum probable individual exposure and the total population exposure.

Of the two estimates, the total population exposure to *p*-toluidine can be more accurately calculated because the certified poundage of D&C Green No. 5 is known. If the average annual certification of D&C Green No. 5 containing 5 ppm of *p*-toluidine (the observed average is less than 3 ppm) is 10,000 pounds, then the average lifetime exposure to *p*-toluidine would be less than 0.27 nanograms (ng) per day per person, or if all of these products were consumed by only 10 percent of the population, 2.7 ng per day per person.

Although a measure of the total population exposure can be calculated quite simply, the maximum probable individual exposure depends on many factors, including the concentration of *p*-toluidine in products, the types of products used, the amount of product used per application, and the frequency of application.

In section IV C, the agency discussed the principal types of products in which D&C Green No. 5 is used and estimated that lifetime-averaged individual exposure to D&C Green No. 5 (internal or external) would not likely exceed 10 mg per day from the applications (mainly used in ingested drugs) that would be permitted by this regulation. If 5 ppm *p*-toluidine is present in an average sample of D&C Green No. 5, an individual exposed to 10 mg per day of D&C Green No. 5 would have a lifetime-average exposure of 50 nanograms (ng) per day *p*-toluidine. Current known uses of D&C Green No. 5, however, result in a much lower exposure to the color additive. Internal exposure is estimated not to exceed several tenths mg per day (lifetime-averaged). If 5 ppm *p*-toluidine is present in an average sample of D&C Green No. 5, an individual exposed to several tenths mg per day (e.g., 0.5 mg per day) would have a lifetime-averaged exposure of 2.5 ng per day.

2. *Extrapolation of risk.* The second part of the evaluation of the risk presented by *p*-toluidine in D&C Green No. 5 is an extrapolation from the actual compound related incidence (risk) found in animal bioassays to the conditions of probable exposure for humans.

The Weisburger paper reported the results of long-term feeding studies of *p*-toluidine in two rodent species, the mouse and the rat. The bioassay in the rat (male only) showed no evidence of *p*-toluidine-induced tumorigenicity. In the mouse bioassay, however, the incidence of *p*-toluidine-induced hepatomas was statistically significant. Male mice showed much greater sensitivity to hepatoma induction than female mice. Moreover, the tumor incidence per unit dose was higher in the low dose (½ MTD) than in the high dose (MTD) group. Consequently, the highest apparent potency was observed in the ½ MTD treated male mice group of all the experimental groups tested (dose/sex/species groups). Therefore, FDA chose the data on this group to estimate the upper limit of human risk because these data are unlikely to produce an underestimation of the actual risk.

FDA used two slightly different quantitative risk assessment procedures to extrapolate from the dose in the male mouse to the very low doses of possible human exposure. Both of these

procedures are conservative and, therefore, are not likely to underestimate the actual risk from very low doses. The use of different risk extrapolation procedures, conservative to different degrees, provides a range of estimates of the maximum risk (each risk value to be taken in the context of the assumptions and principles on which the particular extrapolation procedure is based) that serves as a basis for the agency to judge whether it is possible to determine to a reasonable certainty that no harm will result from the probable exposure to *p*-toluidine from the intended use of D&C Green No. 5.

One of the procedures FDA employed was the linear proportional model with dosage data expressed as a concentration in the total diet (e.g., ppm) and using the upper 99 percent confidence interval of the observed tumor incidence as described in FDA's March 20, 1979 proposal, "Chemical Compounds in Food-Producing Animals" (44 FR 17070). Under this procedure, the upper limit individual lifetime risk from exposure (oral) to 50 ng per day *p*-toluidine is 1 in 30 million. The second procedure the agency used, also a linear proportional model, estimated the even smaller possibility of risk of lifetime tumor incidence of 1 in 300 million.

Because the lifetime-averaged individual exposure to *p*-toluidine from the use of D&C Green No. 5 in internal and externally applied drugs and cosmetics would not likely exceed 50 ng per day, the agency concludes that there is a reasonable certainty of no harm from the exposure to *p*-toluidine that results from the use of D&C Green No. 5.

In arriving at the conclusion that exposure to *p*-toluidine from the use of D&C Green No. 5 is safe, FDA considered the possibility of exposure to minor amounts of *p*-toluidine impurities as a result of the synthetic process of manufacturing several related color additives. Regulations for three color additives now contain specifications on the maximum amount of *p*-toluidine permitted in the additive. D&C Green No. 6 (21 CFR 74.1206, 74.2206, and 82.1206)—0.1 percent *p*-toluidine, Ext. D&C Violet No. 2 (21 CFR 74.2602a)—0.1 percent *p*-toluidine, and D&C Violet No. 2 (21 CFR 74.1602, 74.2602, and 82.1602)—0.2 percent *p*-toluidine.

Certain other color additives might contain small amounts of *p*-toluidine. A preliminary review of the manufacturing processes of these color additives indicates that the level of *p*-toluidine would be far less than the level found in D&C Green No. 6 (approximately 400 ppm *p*-toluidine was found in D&C Green No. 6). In a recent **Federal Register** document (47 FR 14138; April 2, 1982) FDA assessed the upper limit risk from exposure to *p*-toluidine as a result of use of D&C Green No. 6 to be less than 1 in 15 million to 1 in 150 million in a lifetime and concluded that such exposure was safe. The agency will review thoroughly each of the other *p*-toluidine containing color additives and, if necessary to protect the public health, will propose regulatory action to limit further the cumulative exposure to *p*-toluidine from use of color additives. Regardless of the findings of these reviews, the agency considers the combined risk from exposure to *p*-toluidine from use of D&C Green No. 5 and D&C Green No. 6 to be sufficiently low that the additional exposure to *p*-toluidine from the other color additives would not affect its evaluation that the use of D&C Green No. 5 and D&C Green No. 6 is safe.

In section III, the agency stated that the average *p*-toluidine level in D&C Green No. 5 manufactured in accordance with current good manufacturing practice will not likely exceed 5 ppm. This level was employed in the risk analysis above. In order to ensure that the average level does not exceed 5 ppm, a regulatory specification of 15 pm is being established for the maximum amount of *p*-toluidine that can be present in a certified lot.

V. Conclusion

The agency, following evaluation of available data, concludes that D&C Green No. 5 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.

The agency has determined under 21 CFR 25.24(d)(5) (proposed December 11, 1979; 44 FR 71742) 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.

List of Subjects in 21 CFR Parts 74, 81, and 82

Color additives, Cosmetics, Drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 706(b), (c), and (d), 74 Stat. 399–403 (21 U.S.C. 376(b), (c), and (d)) and the Transitional Provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86–618, sec. 203, 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 (formerly 5.1; see 46 FR 26052; May 11, 1981)), Parts 74, 81, and 82 are amended as follows:

PART 74—LISTING OF COLOR ADDITIVES SUBJECT TO CERTIFICATION

1. Part 74 is amended:

a. By revising § 74.1205, to read as follows:

§ 74.1205 D&C Green No. 5.

(a) *Identity.* (1) The color additive D&C Green No. 5 is principally the disodium salt of 2,2'-(9,10-dihydro-9,10-dioxo-1,4-anthracenediyl)diimino) bis-(5-methylbenzenesulfonic acid) (CAS Reg. No. 4403–90–1).

(2) Color additive mixtures for use in drugs made with D&C Green No. 5 may contain only those diluents that are suitable and those that are listed in Part 73 of this chapter for use in color additive mixtures for coloring drugs.

(b) *Specifications.* (1) D&C Green No. 5 for use in coloring surgical sutures 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 practice:

Sum of volatile matter (at 135° C) and chlorides and sulfates (calculated as sodium salts), not more than 20 percent.
Water insoluble matter, not more than 0.2 percent.
1,4-Dihydroxyanthraquinone, not more than 0.2 percent.
2-Amino-*m*-toluenesulfonic acid, not more than 0.2 percent.
Subsidiary colors, not more than 5 percent.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 3 parts per million.
Total color, not less than 80 percent.

(2) D&C Green No. 5 for use in coloring drugs shall conform to the following specifications and shall be free from impurities other than those named to the extent that such other impurities may be avoided by current good manufacturing practice:

Sum of volatile matter (at 135° C) and chlorides and sulfates (calculated as sodium salts), not more than 20 percent.
Water-insoluble matter, not more than 0.2 percent.
1,4-Dihydroxyanthraquinone, not more than 0.2 percent.
Sulfonated toluidines, total not more than 0.2 percent.
p-Toluidine, not more than 0.0015 percent.
Sum of monosulfonated D&C Green No. 6 and Ext. D&C Violet No. 2, not more than 3 percent.
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 80 percent.

(c) *Use and restrictions.* (1) D&C Green No. 5 may be safely used to color nylon 66 (the copolymer of adipic acid and hexamethylenediamine) and/or nylon 6 (poly-(*e*-caprolactam)) nonabsorbable surgical sutures for use in general surgery, subject to the following restrictions:

(i) The quantity of color additive does not exceed 0.6 percent by weight of the suture.

(ii) When the sutures are used for the purposes specified in their labeling, there is no migration of the color additive to the surrounding tissue.

(iii) If the suture is a new drug, an approved new drug application, under section 505 of the act, is in effect for it.

(2) D&C Green No. 5 may be safely used for coloring drugs generally in amounts consistent with current good manufacturing practice.

(d) *Labeling.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(e) *Certification.* All batches of D&C Green No. 5 shall be certified in accordance with regulations in Part 80 of this chapter.

b. By adding new § 74.2205, to read as follows:

§ 74.2205 D&C Green No. 5.

(a) *Identity and specifications.* The color additive D&C Green No. 5 shall conform in identity and specifications to the requirements of § 74.1205 (a)(1) and (b)(2).

(b) *Uses and restrictions.* D&C Green No. 5 may be safely used for color cosmetics generally except in the area of the eye in amounts consistent with current good manufacturing practice.

(c) *Labeling requirements.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Certification.* All batches of D&C Green No. 5 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

2. Part 81 is amended:

§ 81.1 [Amended]

a. In § 81.1 *Provisional lists of color additives* in paragraph (b) by removing the entry "D&C Green No. 5" from the table.

§ 81.27 [Amended]

b. In § 81.27 *Conditions of provisional listing* in paragraph (d) by removing the entry "D&C Green No. 5" from the table.

PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

3. Part 82 is amended by revising § 82.1205, to read as follows:

§ 82.1205 D&C Green No. 5.

The color additive D&C Green No. 5 shall conform in identity and specifications to the requirements of § 74.1205(a)(1) and (b)(2) of this chapter.

Any person who will be adversely affected by the foregoing final rule may at any time on or before July 6, 1982, submit to the Dockets Management Branch (address above), written objections thereto. Objections shall show how the person filing will be adversely affected by the final rule, specify with particularity the provisions of the final rule considered objectionable, and state the grounds for the objections. Objections shall be filed in accordance with the requirements of 21 CFR 71.30. If a hearing is requested, the objections shall state the issue for the hearing, shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Three copies of all documents shall be filed and should be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the final rule may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This final rule shall become effective July 7, 1982, except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack thereof will be announced by publication in the **Federal Register.**

(Sec. 706(c), (c), and (d), 74 Stat. 399–403 (21 U.S.C. 376(b), (c), and (d)); sec. 203, Pub. L. 86–618, Stat. 404–407 (21 U.S.C. 376, note))

Dated: May 27, 1982.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

[FR Doc. 82–14966 Filed 5–28–82; 11:32 am]

BILLING CODE 4160–01–M

21 CFR Part 81

[Docket No. 76N–0366]

Provisional Listing of D&C Green No. 5; Postponement of Closing Date

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is postponing the closing date for the provisional listing of D&C Green No. 5 for use as a color additive in internally ingested and externally applied drugs and cosmetics. A new closing date for D&C Green No. 5 is being established to provide for receipt and evaluation of any objections submitted in response to the final regulation approving the petition for the listing of D&C Green No. 5 for these uses. The regulation that lists D&C Green No. 5 is published elsewhere in this issue of the **Federal Register.**

DATES: Effective May 27, 1982, the new closing date of D&C Green No. 5 will be September 2, 1982.

FOR FURTHER INFORMATION CONTACT: Rudolph Harris, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202–472–5690.

SUPPLEMENTARY INFORMATION: The current closing date of May 30, 1982, for the provisional listing of D&C Green No. 5 was established by notice published in the **Federal Register** of March 27, 1981 (46 FR 18958). The May 30, 1982 closing date for D&C Green No. 5 was established to provide time for determining the applicability of the statutory standard for the listing of color additives to the results of scientific investigations of D&C Green No. 5.

After reviewing and evaluating the data, the agency has concluded that D&C Green No. 5 is safe for these uses. Therefore, elsewhere in this issue of the **Federal Register**, FDA is publishing a regulation that lists D&C Green No. 5.

The regulation set forth below will postpone the May 30, 1982 closing date for the provisional listing of that color additive until September 2, 1982. This postponement will provide sufficient time for receipt and evaluation of comments or objections submitted in response to the regulation that lists D&C Green No. 5 for use in internally ingested and externally applied drugs and cosmetics.

Because of the shortness of time until the May 30, 1982 closing date, FDA concludes that notice and public procedure on this regulation are impracticable. Moreover, good cause exists for issuing this postponement as a