23. Section 388.20(c)(1)(i) is revised to read as follows:

§ 388.20 Record for decision and availability of documents.

* * * * *

(c) *Availability of documents.*—(1) *Scope.*

(i) For proceedings started on or after October 12, 1979, all charging letters, answers, decisions, and orders disposing of a case shall be made available for public inspection in the International Trade Administration Freedom of Information Records Inspection Facility, Room 4001–B, U.S. Department of Commerce. The complete record for decision, as defined in § 388.20 (a) and (b), shall be made available on request. In addition, all decisions on appeal and those final orders providing for denial, suspension or revocation of export licensing privileges shall be published in the **Federal Register.**

* * * * *

24. Section 388.22(b) is revised to read as follows:

§ 388.22 Appeals.

* * * * *

(b) *Filing of appeal.* An appeal of an order must be filed with the Office of the Assistant Secretary for Trade Administration, U.S. Department of Commerce, 14th Street and Constitution Avenue, N.W., Room 3898–B, Washington, D.C. 20230, within 30 days after service of the order appealed from. If the Assistant Secretary cannot act on an appeal for any reason, the Under Secretary for International Trade may designate another Department of Commerce official to receive and act on the appeal.

* * * * *

(Secs. 8, 13, 15, and 21, Pub. L. 96–72, 93 Stat. 503, 50 U.S.C. app. 2401 et seq. (Supp. III 1979); Executive Order No. 12214 (45 FR 29783, May 6, 1980); Department Organization Order 10–3 (unpublished) as reissued February 15, 1982; International Trade Administration Organization and Function Orders 41–1 of February 15, 1982 and 41–4 (47 FR 29582, July 7, 1982)

Date: December 10, 1982.

Bohdan Denysyk,

Deputy Assistant Secretary for Export Administration.

Dated: December 10, 1982.

Theodore Wu,

Deputy Assistant Secretary for Export Enforcement.

[FR Doc. 82–35174 Filed 12–27–82; 8:45 am]

BILLING CODE 3510–25–M

SECURITIES AND EXCHANGE COMMISSION

17 CFR Part 240

[Release No. 34–19336; S7–933]

Pro Rata Rule

AGENCY: Securities and Exchange Commission.

ACTION: Final rule.

SUMMARY: The Commission announces the adoption of revised Rule 14d–8 to govern the acceptance of securities deposited in response to a partial tender offer if a greater number of securities are deposited than the bidder is bound or willing to purchase and rescission of current Rule 14d–8. Pursuant to revised Rule 14d–8, a bidder in an oversubscribed partial tender offer is required to accept securities on a pro rata basis according to the number of securities deposited by each depositor during the period such offer remains open.

DATE: Revised Rule 14d–8 shall be effective with respect to any tender offer subject to Section 14(d) of the Exchange Act that is commenced within the meaning of Rule 14d–2 under that Act after December 28, 1982.

FOR FURTHER INFORMATION CONTACT: Joseph G. Connolly, Jr., (202) 272–3097, Office of Tender Offers, Division of Corporation Finance, Securities and Exchange Commission, 450 Fifth Street, N.W., Washington, D.C. 20549.

SUPPLEMENTARY INFORMATION: The Commission announces the adoption of revised Rule 14d–8 under Sections 14(e) and 23(a) of the Securities Exchange Act of 1934 (the "Exchange Act") (15 U.S.C. 78a *et seq.*). The revised rule requires a bidder in an oversubscribed partial tender offer to accept securities on a pro rata basis according to the number of securities deposited by each security holder during the period such offer remains open.

I. General

After consideration of the comments received on proposed Rule 14d–8,[1] published in Release No. 34–18761 (May 25, 1982) (47 FR 24338) (the "Proposing Release"), and its continuing experience with the ten calendar day proration period in recent partial tender offers, the Commission has determined to adopt revised Rule 14d–8, as proposed, and to rescind current Rule 14d–8 (17 CFR 240.14d–8).[2] The Commission believes that, as stated in the Proposing Release, extension of proration rights throughout the term of the offer is essential to assure security holders the time necessary to consider the merits of an offer and to obtain sufficient information upon which to base their investment decisions and to minimize the potential security holder confusion and misunderstanding generated by changing proration periods and multiple proration pools.

In the Proposing Release, the Commission discussed at length the problems associated with the current ten calendar day proration period and requested comments on its proposal to extend the proration period for the duration of the offer. Concurring in the Commission's assessment that, as used in recent partial tender offers, the minimum ten calendar day proration period denies security holders an adequate opportunity to make informed investment decisions and leads to security holder confusion and misunderstanding, the majority of the commentators supported the Commission's proposal to extend the proration period beyond the current ten calendar day period.

A number of commentators related specific experiences in which they had problems receiving tender offer materials and effecting their investment decisions within the ten calendar day proration period. These experiences included receiving tender offer materials after the expiration of a bidder's proration period or so close to the end of the period that they could not tender before the expiration of the proration period. As a result, these commentators stated that they were foreclosed from participating in the offer and were likely to receive a lesser amount for their securities in a proposed second-step merger. In addition, these commentators highlighted the problems that individual security holders experience trying to understand the varying legal consequences of the deadlines contained in a partial tender offer, appreciating the importance of deciding

[1] Pursuant to the Commission's request for comment on the Proposing Release, 41 commentators submitted 42 letters. The commentators may be categorized as follows: corporations (7); law firms and associations (7); securities industry (6); banks and depositories (2); state governmental agencies (1); academicians (4); and individuals (14). The comment letters are available for public inspection and copying at the Commission's Public Reference Room (*see* File No. S7–933). The Commission also has placed in the files a copy of the summary of public comments prepared by the Division of Corporation Finance.

[2] Having considered the comments received regarding its authority to adopt revised Rule 14d–8, the Commission continues to believe that Sections 14(e) and 23(a) provide such authority.

before the expiration of the proration period whether to tender, sell or hold their stock, and comprehending the effect of multiple proration pools.

Some commentators, while favoring extension of the ten day proration period, suggested modifications to the Commission's specific proposal that were designed principally to make the proration period co-extensive with the withdrawal period. These alternatives were proposed as a result of the commentators' concern that the Commission's proposal would preclude any "early pay" in partial tender offers, since bidders in such offers no longer would be able to begin purchasing tendered securities upon the expiration of the withdrawal period but would have to wait until the expiration of the offer.[3] These commentators expressed concern that the Commission's proposal would tip the balance of advantage in favor of any and all offers and would preclude parity between the two types of offers, because bidders in any and all offers generally could still begin purchasing tendered securities upon the expiration of the withdrawal period.

After reviewing these proposed alternatives, the Commission has concluded that such revisions would continue to deny security holders in a partial tender offer the minimum time prescribed under the tender offer regulations for security holders to make their investment decision, which minimum time is, in fact, assured security holders in an any and all offer. Moreover, the commentators' suggested alternatives fail to eliminate the possibility of multiple proration pools and therefore would permit the current complexity and confusion generated in these partial offers to continue unabated.[4]

[3] Currently, a bidder in a partial offer generally can choose to accept shares for payment upon the expiration of the withdrawal period so long as the shares to be accepted for purchase are not in an open proration pool. In an any and all offer, a bidder generally may choose to accept shares for payment as soon as the withdrawal period expires. In either case, acceptance of securities for payment may be further delayed by, among other things, waiting periods under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 [15 U.S.C. 12 *et seq.*] and required regulatory and shareholders' approvals

[4] Two other proposed alternatives designed to provide some parity between "any and all" and "partial offers" included a suggestion that in addition to extending the proration period for the duration of the offer, the Commission should extend the withdrawal period for the duration of the offer. The other suggestion was to make the proration period co-extensive with the offering period, but allow a bidder to elect to purchase a portion of the shares tendered by each security holder at the time that it would be entitled to purchase securities tendered if the offer were for all the securities. Under this alternative, a bidder at such time could purchase from each security holder a number of shares equal to the percentage of securities of the class sought. The Commission does not believe that achieving time of payment parity between the two types of offers justifies the additional regulation embodied in the first proposal or the increased complexity that would result in the second proposal (particularly in view of the limited utility of such "early pay" option).

II. Certain Findings

As required by Section 23(a)(2) of the Exchange Act, the Commission has specifically considered the impact that the rule will have on competition. The Commission finds that compliance with the rule will not impose a significant burden on competition which is not necessary and appropriate to achieve the purposes of the Exchange Act.

The Commission for good cause finds, in accordance with the Administrative Procedure Act (5 U.S.C. 553(d)), that, in view of the pressing need to address the problems caused by the current ten calendar day proration period, revised Rule 14d–8 should be effective with respect to any tender offer subject to Section 14(d) of the Exchange Act commenced within the meaning of Rule 14d–2 under that Act after the date of publication of revised Rule 14d–8 in the **Federal Register.**

List of Subjects in 17 CFR Part 240

Reporting requirements, Securities.

III. Text of Rule

In accordance with the foregoing, Title 17, Chapter 2, of the Code of Federal Regulations is amended as follows:

PART 240—GENERAL RULES AND REGULATIONS, SECURITIES EXCHANGE ACT OF 1934

1. By revising Rule 14d–8, § 240.14d–8, to read as follows:

§ 240.14d–8 Exemption from statutory pro rata requirements.

Notwithstanding the pro rata provisions of Section 14(d)(6) of the Act, if any person makes a tender offer or request or invitation for tenders, for less than all of the outstanding equity securities of a class, and if a greater number of securities are deposited pursuant thereto than such person is bound or willing to take up and pay for, the securities taken up and paid for shall be taken up and paid for as nearly as may be pro rata, disregarding fractions, according to the number of securities deposited by each depositor during the period such offer, request or invitation remains open.

Authority: This rule is amended pursuant to Sections 14(e) and 23(a) of the Securities Exchange Act of 1934.

(Sec. 23, 48 Stat. 901; sec. 203(a), 49 Stat. 704; sec. 8, 49 Stat. 1379; sec. 10, 78 Stat. 580; sec. 3, 82 Stat. 455; secs. 3–5, 84 Stat. 1497; sec. 18, 89 Stat. 155; 15 U.S.C. 78n(e), 78w(a))

By the Commission (Commissioners Evans, Thomas and Longstreth concurring; Chairman Shad and Commissioner Treadway dissenting).

George A. Fitzsimmons,

Secretary.

December 15, 1982.

Dissent by Chairman Shad:

On December 15th the Commission adopted Rule 14d–8 by a three-to-two vote. This rule extends the minimum proration period for the life of tender offers—from 10 calendar to 20 business days (26 to 28 calendar days). It is intended to reduce public shareholders' confusion and afford them more time to consider and act upon tender offers.

I share the majority's concerns for public shareholders, but dissented briefly for the following reasons.

I. Authority

The Commission's legal authority to extend the statutory proration period is not clear. In addition to the reasons cited by Commissioner Treadway in his dissent, when Congress adopted Section 14(d)(6) of the Securities Exchange Act in 1968, it considered and explicity rejected the proration scheme the new Rule 14d–8 implements.[1] The Supreme Court has held that where the provisions of an Act are unambiguous and its directions specific, there is no power to amend it by regulation[2]; and that if the passage of time indicates changes are needed in a congressionally established regulatory scheme, an agency must go to Congress, rather than implement changes by regulation.[3]

II. Merits

The minimum time periods of the old rule (Section 14(d)(6)) and the new Rule 14d–8 are as follows:

	Minimum business (calendar) days		
	Proration	Withdrawal	Termination
Old rule	6–8 (10)	15 (19–21)	20 (26–28)
New rule	20 (26–28)	15 (19–21)	20 (26–28)

Changes in a tender offer and competitive offers may extend certain of the above time periods, which would compound the problems discussed below.

The new rule increases the proration uncertainty (i.e., risk) to all shareholders, bidder and target companies from 10 to 26–28 calendar days.

Under the old rule, after the 10th calendar day shareholders could redeploy the shares not accepted or sell them and reinvest the

[1] S. Rep. No. 550, 90th Cong., 1st Sess. 4–5 (1967).

[2] *Koshland* v. *Helvering*, 298 U.S. 441, 447 (1936).

[3] *H.K. Porter Co., Inc.* v. *National Labor Relations Board*, 397 U.S. 99, 109 (1970); *Addison* v. *Holly Hill Co.* 322 U.S. 607, 617 (1944).

proceeds in more attractive securities. Under the new rule, they must wait 26–28 calendar days to learn the proration. Such a 16 to 18 day delay circumscribes shareholders' options.

Under the old rule, after the 15 business day withdrawal period, the bidder could purchase the shares tendered. Under the new rule, the bidder must wait an additional week, which increases the bidder's exposure to target defensive tactics, "white knights" and competitive bidders.

Under the old rule, shareholders had 9–11 calendar days after learning the proration to decide whether to withdraw all or any portion of their shares in order to: (a) Tender them to a competitive bidder; (b) sell them and reinvest the proceeds in more attractive securities; or (c) avoid an over-subscription.[4] Under the new rule, the withdrawal period expires five business days *before* shareholders know the proration.

Extending the proration period five business days *beyond* the withdrawal period largely nullifies the benefit of the withdrawal period to shareholders. It also locks-in those who do not withdraw their shares by the 15th business day or who tender thereafter. Therefore, sophisticated shareholders will maximize their options by not tendering until the 20th business day, since there is no advantage in tendering earlier. Unsophisticated shareholders who tender earlier will be locked-in upon expiration of the withdrawal period. In addition, a large volume of last minute tenders will further compound the uncertainty for all shareholders, bidder and target companies.

The new rule does not address dilatory tactics by target companies in forwarding tender offer materials to their shareholders, nor so-called "golder parachutes", nor does it inhibit multiple tenders and proration polls, two-tier offers or legal and financial maneuvers by bidder and target companies. To the contrary, the longer proration period and last minute tenders will facilitate such activities and tend to compound unsophisticated investors' confusion, which will work to the advantage of sophisticated traders.

For example, the much longer proration period, greater uncertainty as to the ultimate proration, increased likelihood of a smaller percentage of the shares tendered being accepted and the increased risk of blocking legal actions by the participants can be expected to result in lower bids in the open market for the public's shares during the longer proration period (nearly a month). This will afford risk arbitrageurs over two extra weeks to accumulate more shares from the public in the open market at lower relative prices than heretofore. The net result may prove to be no greater (if not less) public shareholder participation in proration pools,[5] and lower aggregate price realizations by public shareholders.

The longer proration period and greater uncertainty also increase the risks to first bidders. All other things being equal, this will result in fewer tender offers, to the detriment of public shareholders. Also, if first bidders raise or extend their offers, they will afford more time for competitive bidders and defensive tactics by target companies.

For the foregoing reasons, the new rule also increases potential bidders incentive to accumulate more shares in the open market, prior to announcement of tender offers at higher prices.

III. Study

At the December 15th meeting, the Commission also unanimously approved a study of the foregoing and other aspects or tender offers. Such a study should help clarify these complex issues.

Dissent by Commissioner Treadway:

I respectively dissent from the adoption of Rule 14d–8 under the Securities Exchange Act of 1934. My dissent is based upon my analysis and belief that, as a matter of sound statutory construction, the Commission lacks the authority to adopt the rule.

Rule 14d–8 would modify Section 14(d)(6) of the Securities Exchange Act, which contains an express, unambiguous 10 day proration period. Section 14(d)(6) does not—expressly or implicity—authorize the Commission to modify the 10 day period by rulemaking or order. By way of contrast, the immediately preceding subsection, Section 14(d)(5), which deals with withdrawal rights, expressly confers upon the Commission the authority to modify by rule, regulation or order the time period defined in that subsection. In 1968 Congress specifically considered and rejected conferring upon the Commission such authority in Section 14(d)(6). The difference between the two sections demonstrates that Congress is quite capable of clearly granting us authority to modify expressly stated time frames when that is the intent of Congress.

In 1970, subsequent to the original adoption of Section 14(d)(6), the Congress adopted Section 14(e) under the Securities Exchange Act of 1934. That section provides that the Commission "shall for purposes of this subsection (Section 14(e)), by rules and regulation define and prescribe means reasonably designed to prevent, such acts and practices as are fraudulent, deceptive, or manipulative." The legislative history of Section 14(e) does not address specifically its effect on or relation to Section 14(d)(6) and the express, unambiguous 10 day period contained therein. To conclude that Section 14(e), adopted in 1970, permits the Commission to adopt Rule 14d–8 and thereby override by regulation the statutory 10 day period of Section 14(d)(6), requires that the Commission make a determination that compliance with the express 10 day period of Section 14(d)(6) either is, or is at least closely akin to, "fraudulent, deceptive or manipulative" activity. Confusion and activities which have been characterized as "gamesmenship" in connection with tender offers may not be desirable, but such activities do not, in my view, rise to a level of "fraudulent, deceptive or manipulative" activity, the activities which Section 14(e) is intended to address.

On the basis of the foregoing, I dissent from the Commission's adoption of Rule 14d–8.

[FR Doc. 82–35207 Filed 12–27–82; 8:45 am]
BILLING CODE 8010–01–M

[4] As a result of having hedge tendered (i.e., tendered all the shares they owned and sold additional shares short in the open market).

[5] There is no empirical evidence as to the extent to which public shareholders have been precluded from participating in proration pools under the old rule. The examples cited have been a negligible fraction of the shareholders involved.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 74, 81, and 82

[Docket No. 82N–0378]

D&C Red No. 6 and D&C Red No. 7

AGENCY: Food and Drug Administration.

ACTION: Final rules.

SUMMARY: The Food and Drug Administration (FDA) is "permanently" listing D&C Red No. 6 and D&C Red No. 7 for general use in drugs and cosmetics, except for use in the area of the eye. This action is in response to a petition filed by the Cosmetic, Toiletry and Fragrance Association, Inc. This rule will remove D&C Red No. 6 and D&C Red No. 7 from the provisional list of color additives for use in drugs and cosmetics. Published elsewhere in this issue of the **Federal Register** is an order extending the closing date for the provisional listing of D&C Red No. 6 and D&C Red No. 7 until March 29, 1983.

DATES: Effective January 28, 1983; objections by January 27, 1983.

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: John L. Herrman, Bureau of Foods (HFF–334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204; 202–472–5690.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 6, 1973 (38 FR 21199), FDA announced that a petition (CAP 5C0040) for the permanent listing of D&C Red No. 6 and D&C Red No. 7 as color additives for use in drugs and cosmetics had been filed by the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), 1110 Vermont Ave. NW., Washington, DC 20005.

The petition was filed under section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376). A later notice in the **Federal Register** of March 5, 1976 (41 FR 9584), amended the notice of filing of the petition to include the use of D&C Red No. 7 in cosmetics intended for use in the area of the eye.

D&C Red No. 6 is principally the disodium salt of 3-hydroxy-4-[(4-methyl-2-sulfophenyl)azo]-2-naphthalenecarboxylic acid. D&C Red No. 7 is the calcium salt of the same compound.

I. Toxicological Testing of D&C Red No. 6 and D&C Red No. 7

The provisional regulations published in the **Federal Register** of February 4, 1977 (42 FR 6992) required new chronic toxicity studies of D&C Red No. 6 and D&C Red No. 7 as a condition for their continued provisional listing. FDA placed these requirements on 32 color additives, including D&C Red No. 6 and D&C Red No. 7, because the toxicity studies 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 41863; Docket No. 76N–0366):

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 on the chronic toxicity or carcinogenic potential of the color additive. 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.

FDA postponed the closing date for the provisional listing of the color additives until January 31, 1981, for the completion of required toxicity studies. FDA later extended the closing date for completing these studies and for submitting data. In a proposal published in the **Federal Register** of November 14, 1980 (45 FR 75226), the agency outlined the reasons for postponing the closing dates for 23 provisionally listed color additives under test, including D&C Red No. 6 and D&C Red No. 7, beyond January 31, 1981.

In the **Federal Register** of March 27, 1981 (46 FR 18954), the agency established a new closing date of December 31, 1982, for the complete evaluation of D&C Red No. 6 and D&C Red No. 7. When the order set forth below becomes effective, it will remove D&C Red No. 6 and D&C Red No. 7 from the provisional list. Published elsewhere in this issue of the **Federal Register** is an order extending the closing date for the provisional listing of D&C Red No. 6 and D&C Red No. 7 until March 29, 1983, to provide an opportunity for filing objections to this order.

II. Chemistry Concerns

The provisional regulations of February 4, 1977, also established a closing date of October 31, 1977, for developing the chemistry data and analytical methods necessary for defining chemical specifications for certifying batches of D&C Red No. 6 and D&C Red No. 7. FDA requires chemical specifications, based on appropriate analytical methods, that are sufficiently precise that the agency can certify that batches of each color additive are equivalent to the batches of the color additive used in the animal studies that established the safety of the color additive.

The petitioner has been actively engaged in efforts to provide the chemistry information needed to establish specifications since submitting the petition to the agency. By 1977 experimental data showed that both D&C Red No. 6 and D&C Red No. 7 contained unidentified material, but the agency did not have sufficient information to establish appropriate specifications. FDA expected that the chemical nature and amount of this unidentified material, which is soluble in ether, could be established before October 31, 1977. However, this task proved to be more difficult to complete than expected and could not be completed during the short postponement period. FDA, therefore, extended the closing date to October 31, 1978, under § 81.27(c) (21 CFR 81.27(c)), for the development of the necessary chemistry data and analytical methods for the color additives (43 FR 14642; April 7, 1978).

III. Resolution of Concerns Relating to Unidentified Material

FDA has evaluated the scientific data regarding the chemical characterization of D&C Red No. 6 and D&C Red No. 7. Although the petitioner was unable to determine the chemical identity of the material in the ether layer, spectrophotometric analysis provides a means of measuring the total amount of this component that may be present in each batch of these color additives. FDA concludes that samples submitted for certification can be compared spectrophotometrically with samples of the batches tested toxicologically. By this procedure, the agency can assure that certified batches, on average, will not contain a higher percentage of the unknown material than those tested for safety in the chronic toxicity studies. The feeding studies establish that the color additives are safe when the ether-soluble material is present at this level. Therefore, a test specification for ether-soluble matter is included in the regulations. The method for this test is published as an Appendix A to this final rule.

IV. Potential Impurities in D&C Red No. 6 and D&C Red No. 7

The principal starting materials for the manufacture of D&C Red No. 6 and D&C Red No. 7 are *p*-toluidine *m*-sulfonic acid (PTMSA) and 3-hydroxy-2-naphthoic acid. PTMSA may contain small amounts of *p*-toluidine and even smaller amounts of *o*-toluidine. FDA became concerned about these potential impurities when *o*-toluidine (Ref. 1) and *p*-toluidine (Ref. 2) were reported to be animal carcinogens.

FDA and CTFA have concentrated their efforts on finding suitable methods to measure *p*-toluidine rather than *o*-toluidine because *o*-toluidine is present only as a contaminant of *p*-toluidine. *o*-Toluidine would thus be present in the color additive at levels that are vanishingly small. In fact, *o*-toluidine has never been detected in either color additive.

CTFA has submitted to FDA a report containing a method prepared by Shiseido Laboratories (Yokohama, Japan) for determining residual *p*-toluidine in D&C Red No. 6. The method submitted by Shiseido Laboratories uses high performance liquid chromatography separation with fluorescence detection. The reported limit of detection for this method is 0.2 part per million (ppm). FDA considers that this method is a valid analytical method for determining residual *p*-toluidine levels in D&C Red No. 6 at least to 1.5 ppm and probably lower. In addition, FDA has developed a high performance liquid chromatography method for detecting *p*-toluidine in D&C Red No. 6 and D&C Red No. 7 with a reliable sensitivity of less than 5 ppm.

Using the high performance liquid chromatography method that it developed, Shiseido Laboratories analyzed the residual *p*-toluidine in samples of two commercial batches of D&C Red No. 6 sold in the United States. Shiseido Laboratories reported *p*-toluidine levels for these samples of 0.63 and 2.25 ppm. FDA has examined two additional batches of D&C Red No. 6 and one batch of D&C Red No. 7. The largest amount of *p*-toluidine present in

these samples appeared to be less than 2 ppm. Based on these analytical results, FDA expects that the average *p*-toluidine level in certified D&C Red No. 6 and D&C Red No. 7 prepared in accordance with current good manufacturing practice will not exceed 5 ppm.

To ensure that future batches of these color additives are produced in accordance with current good manufacturing practice, FDA is setting a specification of 15 ppm *p*-toluidine in these regulations. This level of *p*-toluidine can be readily detected by practical methods and thus will ensure that no batch will contain excessive amounts of *p*-toluidine. The agency also considers that this specification will provide adequate control for residual *o*-toluidine because, as a contaminant of *p*-toluidine, the amount of *o*-toluidine present is dependent on the amount of *p*-toluidine present. The agency's evaluation of the safety of D&C Red No. 6 and D&C Red No. 7 containing *p*-toluidine impurities is discussed in section V. below.

V. Evaluation of the Safety of D&C Red No. 6 and D&C Red No. 7 for Drug and Cosmetic Use

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 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 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. Rep. 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 (21 U.S.C. 376(b)(5)(B)), which provides that a color additive 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. *Results of toxicology studies.* The agency has completed its evaluation of the color additive petition for D&C Red No. 6 and D&C Red No. 7, including two new chronic toxicity studies on D&C Red No. 6 in rats and mice. These new long-term 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 significantly increases the power of these tests to detect dose-related effects. The studies were designed and conducted in full compliance with the agency's good laboratory practice regulations and were subject to inspections by FDA officials during their course.

The test material in the recent chronic rat and mouse studies was D&C Red No. 6. Because D&C Red No. 6 and D&C Red No. 7 are the disodium and the calcium salts, respectively, of the same compound, the agency considers the two color additives to be toxicologically equivalent. Thus, any safety conclusion drawn from studies of either color additive applies equally to the other.

Before 1977, the petitioner had submitted reports on a number of animal toxicity studies with D&C Red No. 7. Among these studies were 2-year feeding studies in rats and dogs, a three-generation reproduction study in rats, a repeated dermal application study in rabbits, a lifetime skin-painting study in mice, teratology studies in rats and rabbits, subacute feeding studies in rats and dogs, and acute oral toxicity studies in rats and dogs. These studies did not produce any evidence that the use of these color additives for the petitioned uses would be unsafe.

However, FDA did note a treatment-related effect in the three-generation reproduction study in which rats received D&C Red No. 7 in the diet at dosage levels of 0.5, 5.0, 15.0, and 50.0 milligrams per kilogram (mg/kg). At the higher dose level, the second generation rats, but not the first or third generation, had decreased fertility. No treatment-related effects were observed at any other dose level. Accordingly, FDA set the no-adverse-effect level in this study at the next lower dose level, which was 15 milligrams D&C Red No. 7 per kilogram body weight per day (15 mg/kg/day).

As discussed above, in 1976, the agency concluded that new chronic toxicity feeding studies would be required to provide data to permit a final determination to be made on the listing of D&C Red No. 6 and D&C Red No. 7 (41 FR 41860; September 23, 1976). These new chronic studies revealed two treatment-related effects from ingestion of D&C Red No. 6.

In one new chronic feeding study, male and female CD–1 mice were fed diets containing D&C Red No. 6 at concentrations of 0.05, 1.0, and 5.0 percent of their diets. The only treatment-related effect in this study was decreased survival of high-dose male mice, compared to controls, during the last 6 months of the study. No carcinogenic effects or other changes that could be ascribed to treatment of mice with D&C Red No. 6 were observed.

In the other new chronic feeding study, which was with male and female Charles River CD rats, parental animals were fed diets containing D&C Red No. 6 at concentrations of 0.05, 0.30, and 2.0 percent continuously from before mating until weaning of their offspring. The offspring were fed diets containing these same concentrations of D&C Red No. 6 for 24 months in males and 31 months in females. The agency noted an increased incidence of kidney disease, listed as chronic nephritis by the testing laboratory, in both male and female rats at the high-dose level. To resolve questions about this kidney disease, FDA requested, by letter dated August 19, 1982, microslides from tissue sections of the kidneys of all rats from the two control groups and the three groups fed diets containing D&C Red No. 6.

The examination of slides by FDA pathologists revealed a treatment-related effect on a commonly occurring spontaneous disease of rats known as

chronic progressive nephrosis. The occurrence of chronic progressive nephrosis as observed in this study was graded by the agency pathologists as being minimal, mild, moderate, or severe. There was no significant difference between the control and treated groups, for both male and female rats, in the incidence of chronic progressive nephrosis that was of minimal to mild severity. However, there was an increased incidence of moderate to severe chronic progressive nephrosis among the male rats in the mid- and high-dose groups compared to the male rats in the low-dose or control groups. Similarly, the incidence of moderate to severe chronic progressive nephrosis was increased among high-dose group female rats compared to the incidence of this effect among other treated or control group female rats. Agency pathologists concluded that, although there were no carcinogenic renal changes in this study attributable to the administration of D&C Red No. 6, there appeared to be an exacerbation of a spontaneous renal disease of aged rats (chronic progressive nephrosis) in the mid- and high-dose group male rats and in the high-dose group female rats.

C. *Computation of acceptable daily intake.* FDA calculates the acceptable daily intake for a color additive by using the following process: The agency identifies the highest no-adverse-effect level in each study in which it observes a treatment-related effect. It then compares the no-adverse-effect levels from these studies and uses appropriate safety factors (see 21 CFR 70.40) to calculate the acceptable daily intake for the color additive using the study that leads to the lowest value.

In the chronic feeding study with mice, the mid-dose (1500 mg/kg/day) was the no-adverse-effect level, and in the chronic feeding study with rats, the low dose (25 mg/kg/day) was the no-adverse-effect level.

Of the effects noted in all the studies reviewed by the agency, the three-generation reproduction study in rats establishes the lowest acceptable daily intake for D&C Red No. 6 and D&C Red No. 7. The no-adverse-effect level for this study was 15 mg/kg/day. Reduced by the safety factor of 100, this study establishes an acceptable daily intake of 0.15 mg/kg/day, or 9 mg/day for a 60 kg human.

D. *Prior actions by FDA.* Even though appropriate testing of D&C Red No. 6 and D&C Red No. 7 did not show them to be carcinogens, the agency still had to consider whether to list these color additives in light of the fact that they contain carcinogenic impurities, *p*-toluidine and *o*-toluidine. In the past, FDA has terminated the provisional listings of several color additives that contained or were expected to contain a carcinogenic impurity or constituent. (See the D&C Green No. 5 final rule published in the **Federal Register** of June 4, 1982 (47 FR 24278, 24280).) However, the agency no longer believes that it must refuse to list a color additive simply because it contains or is expected to contain a carcinogenic impurity.

As explained in the D&C Green No. 6 final rule (47 FR 14138, 14141–2 (April 2, 1982)), the agency has concluded that even if a color additive contains a carcinogenic impurity, the Delaney Clause is not triggered unless the color additive as a whole is found to cause cancer. 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 the use of a color additive that has not been shown to be a carcinogen but that does contain a carcinogenic impurity. The estimate of the risk may be exaggerated because the extrapolation models used are designed to estimate the maximum risk consistent with the data. For this reason, the estimate can be used with confidence to conclude that a substance is safe under specific conditions of use. (FDA has also explained the basis for this approach in the advance notice of proposed rulemaking on its policy for regulating carcinogenic chemicals in food and color additives published in the **Federal Register** of April 2, 1982 (47 FR 14464).)

Recently, the agency has examined the risk associated with drug and cosmetic uses of D&C Green No. 6 and D&C Green No. 5, which contain minor amounts of *p*-toluidine. Neither color additive had been shown to be carcinogenic by appropriate bioassays. FDA concluded in both instances that the use of these color additives in drugs and cosmetics is safe. The agency is using the same method of analysis for D&C Red No. 6 and D&C Red No. 7.

E. *Use of D&C Red No. 6 and D&C Red No. 7.* Between 1970 and 1977, FDA did not certify any D&C Red No. 6 (straight color), but from 1978 through 1982, FDA certified an average of 560 pounds of this color additive per year. The agency did not certify any straight D&C Red No. 7 during the period of 1970 through 1982.

The use of D&C Red No. 6 and D&C Red No. 7 lakes increased during the second half of the 1970's. The average pounds per year certified for the period 1978 through 1982 was 44,800 pounds of D&C Red No. 6 lakes and 107,300 pounds of D&C Red No. 7 lakes.[1] Based on these average yearly certified poundage data and the trend of increasing use of these color additives, FDA expects that the average total certified poundage of D&C Red No. 6, D&C Red No. 6 lakes, and D&C Red No. 7 lakes might increase to roughly 600, 60,000, and 120,000 pounds per year, respectively. Although individual batches of lakes vary widely in content of primary colors, the average primary color content of the lakes of any specific color additive generally does not exceed 40 percent primary color. Assuming that the average primary color content of lakes is 40 percent, exposure to D&C Red No. 6 and D&C Red No. 7 from both straight color and lake uses would be roughly 72,600 pounds per year.

Many cosmetic manufacturers submit cosmetic product ingredient statements (formulations) to FDA under the voluntary cosmetic regulatory program (21 CFR Part 720). This program provides information on the specific types of cosmetic products in which D&C Red No. 6 and D&C Red No. 7 are 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 9 formulations that listed D&C Red No. 6 as an ingredient, 598 formulations that listed D&C Red No. 6 lakes as ingredients, 45 formulations that listed D&C Red No. 7 as an ingredient, and 1,178 formulations that listed D&C Red No. 7 lakes as ingredients. (Apparently, for at least D&C Red No. 7, some companies reported use of the straight color when they used the lake.) The major uses of D&C Red No. 6 and D&C Red No. 7 and their lakes in cosmetics were in make-up preparations (57.6 percent) and in manicuring preparations (41.4 percent). Of the listed make-up preparations, 69 percent were lipsticks. The levels at which these color additives are used in

[1] This order does not permanently list D&C Red No. 6 and D&C Red No. 7 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. 6 and D&C Red No. 7 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 discussion of the lakes here is solely for the purpose of establishing the level of exposure to these color additives.

lipsticks range from 0.0013 percent to 6.0 percent (straight color).

In a 1965 Pharmaceutical Manufacturers Association survey, 7 companies reported use of D&C Red No. 7 in 19 drug preparations, all for internal administration. The maximum amount of the color additive used by a company was 4.4 milligrams per daily dose of drug, although most companies used much less. There was no reported use of D&C Red No. 6 in drug products.

Although the fraction of D&C Red No. 6 and D&C Red No. 7 used in ingested drugs apparently is minor at this time, use in ingested drugs without a limitation would represent the greatest potential intake for individuals to these color additives, especially over short periods of time. If no limitation were set, use could exceed the acceptable daily intake. FDA has therefore incorporated a limitation of 5 milligrams of D&C Red No. 6 and D&C Red No. 7 per daily dose of drug product under §§ 74.1306 and 74.1307, respectively. This limitation applies both to ingested and externally applied drug products. It will ensure safe use and is consistent with currently known use levels.

The agency has considered several factors in estimating daily intake from the amount of color additives used in drug or cosmetic products. These factors include, for short-term use, the amount of product likely to be used and the amount of product used that would enter the body by, e.g., ingestion of a drug; the fraction of applied lipstick that would be ingested; and the fraction of color additives likely to penetrate skin from external use. These factors vary with the individual product type. For lifetime average intake, the agency has considered the fact that conditions leading to maximum intake on a given day are not likely to exist every day of one's life. Frequency of use will also vary with individual products. Details of the agency's assumptions can be found in Reference 3.

Using these factors the agency estimates that short-term intake of D&C Red No. 6 and D&C Red No. 7 in drugs will not exceed 5 mg/day, and short-term intake to these color additives from cosmetic use will not exceed 3 mg/day, resulting in a cumulative dose of 8 mg/day. For lifetime-average use, the agency estimates 1 mg/day from drug use, 1 mg/day from ingested cosmetic use, and 4 mg/day from external cosmetic use (only a small fraction of which will be absorbed), leading to the agency's estimated lifetime average intake of approximately 2 mg/day. Details of the agency's estimates and calculations can be found in Reference 3.

F. *Application of risk assessment in this rulemaking.* Because *p*-toluidine may be present in D&C Red No. 6 and D&C Red No. 7 in minor amounts, use of these color additives as authorized by these regulations will likely result in exposure to very small amounts of *p*-toluidine. Any residual *p*-toluidine that might be present does not contribute any color to D&C Red No. 6 or D&C Red No. 7, nor does in impart any color to drugs, cosmetics, or the human body. Consequently, FDA concludes that, although a small amount of *p*-toluidine may be added to drugs and cosmetics with the addition of D&C Red No. 6 or D&C Red No. 7, this chemical is not a color additive within the meaning of section 201(t) of the act (21 U.S.C. 321(t)). [2] Instead, *p*-toluidine would be only an impurity in D&C Red No. 6 and D&C Red No. 7. Because D&C Red No. 6 (and hence D&C Red No. 7) has not been shown to be carcinogenic, the agency concludes, as in the D&C Green No. 6 and D&C Green No. 5 rulemaking proceedings, that it can use risk assessment procedures to provide a basis for deciding whether there is a reasonable certainty of no harm from the use of D&C Red No. 6 and D&C Red No. 7 in ingested and externally applied drugs and cosmetics.

The risk evaluation of *p*-toluidine consists of two parts: (1) Assessment of probable exposure to *p*-toluidine from the use of D&C Red No. 6 and D&C Red No. 7 in ingested and externally applied drugs and cosmetics, and (2) extrapolation of the risk from *p*-toluidine observed in the animal biassay to the conditions of probable exposure to 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 these color additives is known. If the average annual certification of D&C Red No. 6 and D&C Red No. 7 (assumed to contain 5 ppm of *p*-toluidine) is 72,600 pounds, then the average lifetime exposure to *p*-toluidine would be less than 2.0 nanograms (ng) per person per day, or if all of the products containing these color additives were consumed by only 10 percent of the population, 20 ng per person per day.

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 the application. In section V.E of this preamble, FDA discussed the principal types of products in which D&C Red No. 6 and D&C Red No. 7 are used. The agency estimates that the combined lifetime-average individual exposure to these color additives from the ingested and external applications permitted by these regulations would not likely exceed 6 milligrams per day (1 milligram per day from drugs and 5 milligrams per day from ingested and externally applied cosmetics (Ref. 3)). This level is higher than the lifetime-average intake value calculated earlier for the color additives because the 6 milligrams per day figure does not correct for limited penetration of these color additives. Thus, in the absence of adequate data regarding skin penetration by *p*-toluidine, the agency is assuming 100 percent skin penetration of *p*-toluidine from externally applied drugs and cosmetics containing these color additives. This estimate is clearly exaggerated, but the exaggeration does not affect the conclusions of the analysis. If 5 ppm *p*-toluidine is present in an average sample of D&C Red No. 6 or D&C Red No. 7, an individual exposed to 6 milligrams per day of these color additives would have a lifetime-average exposure of 30 ng per day *p*-toluidine.

FDA also recognizes the possibility that individuals will be exposed to minor amounts of *p*-toluidine impurities as a result of their use of products containing several related color additives. Regulations for four color additives now contain specifications on the amount of *p*-toluidine permitted in the additive: D&C Green No. 5 (21 CFR 74.1205, 74.2205, and 82.1205)—0.0015 percent *p*-toluidine; 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. The latter three color additives are not permitted for use in ingested products. FDA believes that these are the only color additives that contain *p*-toluidine.

2. *Extrapolation of risk.* The second part of the evaluation of the risk presented by *p*-toluidine in D&C Red No. 6 and D&C Red No. 7 is an extrapolation from the actual compound-related incidence (risk) found in animal

[2] This statement is also true for *o*-toluidine

bioassays to the conditions of probable exposure for humans.

The final rules permanently listing D&C Green No. 5 and D&C Green No. 6 discussed the publication by Weisburger, et al. (Ref. 2), which reported the results of long-term feeding studies of *p*-toluidine in mice and rats. FDA has used the data from the Weisburger paper to estimate the upper level of human risk of exposure to *p*-toluidine from the use of D&C Green No. 5, D&C Green No. 6, and, in this case, D&C Red No. 6 and D&C Red No. 7. The agency used two quantitative risk assessment procedures to extrapolate from the dose in the animal experiment to the very low doses of possible human exposure. Both of these procedures are not likely to underestimate the actual risk from very low doses. They serve as a basis for the agency to determine to a reasonable certainty whether any harm will result from the probable exposure to *p*-toluidine from the use of these color additives.

One of the procedures FDA employed was the linear proportional model with dosage data expressed as a concentration of the total diet 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 to 30 ng per day *p*-toluidine is 1 in 50 million. The second procedure the agency used, also a linear proportional model, estimated the even smaller upper limit risk of lifetime tumor incidence of 1 in 500 million.

Because the lifetime-averaged individual exposure to *p*-toluidine from the use of D&C Red No. 6 and D&C Red No. 7 in drugs and cosmetics would not likely exceed a total of 30 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 these color additives.[3]

FDA has also considered the upper limit of risk from exposure to the several color additives that may contain *p*-toluidine to determine whether any harm will result from the probable cumulative exposure to *p*-toluidine from the intended use of all these color additives.

In the D&C Green No. 6 rulemaking proceeding, FDA assessed the upper limit of 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. Likewise, for D&C Green No. 5, FDA calculated that the upper limit lifetime risk from exposure to *p*-toluidine as a result of use of this color additive is less than 1 in 30 million to 1 in 300 million. In this document, FDA has calculated that the upper limit lifetime risk from exposure to *p*-toluidine as a result of D&C Red No. 6 and D&C Red No. 7 is less than 1 in 50 million to 1 in 500 million.

Detailed risk assessment analyses have not been performed for possible exposure to *p*-toluidine from the use of Ext. D&C Violet No. 2 (21 CFR 74.2602a) and D&C Violet No. 2 (21 CFR 74.1602, 74.2602, and 82.1602). However, FDA estimates that exposure to *p*-toluidine from the use of these color additives is in the same range as with D&C Green No. 6, because use limitations and specifications are similar, providing approximately the same level of risk. The agency finds that the upper limit of combined risk from the use of these color additives is so low that the exposure to *p*-toluidine from the use of these color additives is safe. The agency notes, however, that it is extremely unlikely that any one individual would use all these color additives at the same time and at the maximum levels.

VI. References

The following information has 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 Cancer Institute, "Bioassay of *p*-Toluidine Hydrochloride for Possible Carcinogenicity," NCI Technical Report No. 153, NCI–CG–TR–153, U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, 1979.

2. Weisburger, E. K., et al., "Testing of Twenty-one Environmental Aromatic Amines or Derivatives for Long-term Toxicity or Carcinogenicity," *Journal of Environmental Patholgy and Toxicology*, 2:325–356, 1978.

3. Martin, R. L. and T. C. Troxell, Memorandum for the Record, Color Additive Petition 5C0040, December 20, 1982.

VII. Conclusion

Based upon the evaluation of the results of the two recently submitted chronic toxicity studies, the agency has determined that D&C Red No. 6 (and hence D&C Red No. 7) is not carcinogenic to Charles River Sprague-Dawley CD rats after dietary exposure as high as 2.0 percent or to CD–1 mice after dietary exposure as high as 5.0 percent under conditions of testing adequate to provide assurance for its safe use. FDA has calculated a combined total acceptable daily intake of 9 milligrams per day of D&C Red No. 6 and D&C Red No. 7 for a 60 kg human on the basis of all the toxicity studies it reviewed. The agency finds that short-term intake (8 milligrams per day) and lifetime-averaged intake (2 milligrams per day) from the listed drug and cosmetic uses of these color additives will be within this amount.

The agency has also completed its evaluation of other animal studies submitted by the petitioner for the purpose of establishing the safety of D&C Red No. 6 and D&C Red No. 7 for use in externally applied drugs and externally applied cosmetics. The data from these studies indicate that D&C Red No. 7 is nonirritating when applied daily to either intact or abraded skin. Furthermore, D&C Red No. 7 was not found to be carcinogenic upon twice-weekly application to the skin of mice over their lifetimes.

Therefore, FDA finds that it can conclude that no harm will result from the petitioned uses of D&C Red No. 6 and D&C Red No. 7, for general use in drugs and cosmetics excluding use in the area of the eye, and that certification is necessary for the protection of the public health. The final toxicity study reports, interim reports, and the agency's toxicology 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.

FDA notified the petitioner 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. 7 in cosmetics intended for use in the area of the eye. In the latest letter, dated October 24, 1978, FDA advised the petitioner to consider withdrawing that portion of the petition that sought approval of use of D&C Red No. 7 in cosmetics intended for use in the area of the eye because it appeared that the required data from eye-area studies would not be readily available.

The petitioner has not submitted the data required to support eye-area use of D&C Red No. 7. Therefore, FDA now considers that portion of the petition that was amended by the filing on March 5, 1976 (Docket No. 76C–0044) to include the permanent listing of D&C Red No. 7 for eye-area use to be withdrawn without prejudice in accordance with the provisions of § 71.4 (21 CFR 71.4). Section 71.4 requires that such requested information be submitted within 180 days after filing of the petition, or the petition will be withdrawn without prejudice. Use of

[3] The presence of *o*-toluidine in the color additives would not alter this conclusion. At the levels at which a user of a product containing D&C Red No. 6 or D&C Red No. 7 would be exposed to *o*-toluidine, the presence of this impurity would have virtually no effect on the upper limit of risk.

D&C Red No. 7 in the area of the eye has never been covered by a provisional listing. Future consideration by FDA of the permanent listing of D&C Red No. 7 for eye-area use will require the submission of a new color additive petition for that use. The agency's listing of a color additive for general use in drugs and cosmetics does not encompass eye-area use (see § 70.5 *General restrictions on color additives* (21 CFR 70.5)).

The agency is establishing new chemical specifications that identify the color additives more precisely than those specifications currently in Part 82 (21 CFR Part 82). The agency concludes that it is necessary to include in the listing regulations for D&C Red No. 6 and D&C Red No. 7 a brief description of their manufacturing processes to ensure the safety of the color additives. The agency is concerned that the color additives may contain harmful impurities dependent upon the manufacturing processes used to produce the color additives. The agency is not able at this time to set specifications that would control the presence of these impurities. 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 Chemicals Codex. Similarly, appropriate specifications for color additives for use in drugs and cosmetics will be developed following the general guidelines used by the NAS/NRC in its evaluation of color additives used in food. The agency concludes that specifying, through a general description, the manufacturing process in the regulations for these color additives will provide an adequate assurance of safety until suitable specifications can be developed. Production of the color additives by the specified methods will assure qualitatively similar batches and thus adequately assure the absence of harmful impurities resulting from changes in the manufacturing process.

Also, the chemical names for the two color additives in new listings under 21 CFR Part 74 are different from the names currently listed under 21 CFR Part 82. The agency is listing the nomenclature designated in the Chemical Abstracts Index Guide (September 1982) because the agency believes that it gives the best description of the color additive. FDA is identifying D&C Red No. 6 as the disodium salt, rather than the monosodium salt, as it is currently described in § 82.1306 (21 CFR 82.1306), because analytical results confirm that hydrogens of the carboxylic and sulfonic acid groups are both replaced by sodium.

FDA is also removing § 81.27(c) from its regulations. The agency is making this editorial change because the color additives listed under § 81.27(c) have now been removed from the provisional list. Ferric ferrocyanide was permanently listed for use in drugs and cosmetics under 21 CFR 73.1299 and 73.2299 by a final rule published in the **Federal Register** of November 21, 1978 (43 FR 54235). D&C Red No. 30 was permanently listed for use in drugs and cosmetics under 21 CFR 74.1330 and 74.2330 by a final rule published in the **Federal Register** of May 25, 1982 (47 FR 22509).

The agency has determined under 21 CFR 25.24(b)(12) and (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 environment. Therefore, neither an evironmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 74

Color additives, Color additives subject to certification, Cosmetics, Drugs.

21 CFR Part 81

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

21 CFR Part 82

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

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 706 (b), (c), and (d), 74 Stat. 299–403 (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), 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 adding new § 74.1306 to Subpart B, to read as follows:

§ 74.1306 D&C Red No. 6.

(a) *Identity.* (1) The color additive D&C Red No. 6 is principally the disodium salt of 3-hydroxy-4-[(4-methyl-2-sulfophenyl)azo]-2-naphthalenecarboxylic acid (CAS Reg. No. 5858–81–1). To manufacture the additive, 2-amino-5-methylbenzenesulfonic acid is diazotized with hydrochloric acid and sodium nitrite. The diazo compound is coupled in alkaline medium with 3-hydroxy-2-naphthalenecarboxylic acid. The resulting dye precipitates as the disodium salt.

(2) Color additive mixtures for drug use made with D&C Red No. 6 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.* The color additive D&C Red No. 6 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 10 percent.
Ether-soluble matter, passes test entitled "The Procedure for Determining Ether-Soluble Material in D&C Red Nos. 6 and 7," which is an Appendix A to Part 74.
2-Amino-5-methylbenzenesulfonic acid, sodium salt, not more than 0.2 percent.
3-Hydroxy-2-naphthalenecarboxylic acid, sodium salt, not more than 0.4 percent.
3-Hydroxy-4-[(4-methylphenyl)azo]-2-naphthalenecarboxylic acid, sodium salt, not more than 0.5 percent.
p-Toluidine, not more than 15 parts per million.
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 90 percent.

(c) *Uses and restrictions.* The color additive D&C Red No. 6 may be safely used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 milligrams per daily dose of the drug.

(d) *Labeling.* 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. 6 shall be certified in accordance with regulations in Part 80 of this chapter.

b. By adding new § 74.1307 to Subpart B, to read as follows:

§ 74.1307 D&C Red No. 7.

(a) *Identity.* (1) The color additive D&C Red No. 7 is principally the calcium salt of 3-hydroxy-4-[(4-methyl-2-sulfophenyl)azo]-2-

naphthalenecarboxylic acid (CAS Reg. No. 5281–04–9). To manufacture the additive, 2-amino-5-methylbenzenesulfonic acid is diazotized with hydrochloric acid and sodium nitrite. The diazo compound is coupled in alkaline medium with 3-hydroxy-2-naphthalenecarboxylic acid and the resulting dye converted to the calcium salt with calcium chloride.

(2) Color additive mixtures for drug use made with D&C Red No. 7 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.* The color additive D&C Red No. 7 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 10 percent.
Ether-soluble matter, passes test entitled "The Procedure for Determining Ether-soluble Material in D&C Red Nos. 6 and 7," which is an Appendix A to Part 74.
2-Amino-5-methylbenzenesulfonic acid, calcium salt, not more than 0.2 percent.
3-Hydroxy-2-naphthalenecarboxylic acid, calcium salt, not more than 0.4 percent.
3-Hydroxy-4-[(4-methylphenyl)azo]-2-naphthalenecarboxylic acid, calcium salt, not more than 0.5 percent.
p-Toluidine, not more than 15 parts per million.
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 90 percent.

(c) *Uses and restrictions.* The color additive D&C Red No. 7 may be safely used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 milligrams per daily dose of the drug.

(d) *Labeling.* 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. 7 shall be certified in accordance with regulations in Part 80 of this chapter.

c. By adding new § 74.2306 to Subpart C, to read as follows:

§ 74.2306 D&C Red No. 6.

(a) *Identity and specifications.* The color additive D&C Red No. 6 shall conform in identity and specifications to the requirements of § 74.1306 (a)(1) and (b).

(b) *Uses and restrictions.* The color additive D&C Red No. 6 may be safely used for coloring cosmetics generally 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 Red No. 6 shall be certified in accordance with regulations in Part 80 of this chapter.

d. By adding new § 74.2307 to Subpart C, to read as follows:

§ 74.2307 D&C Red No. 7

(a) *Identify and specifications.* The color additive D&C Red No. 7 shall conform in identity and specifications to the requirements of § 74.1307 (a)(1) and (b).

(b) *Uses and restrictions.* The color additive D&C Red No. 7 may be safely used for coloring cosmetics generally 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 Red No. 7 shall be certified in accordance with regulations in Part 80 of this chapter.

e. By adding new Appendix A to Part 74 to read as follows:

Appendix A to Part 74—The Procedure for Determining Ether Soluble Material in D&C Red Nos. 6 and 7

The dye is dissolved in glacial acetic and 8 *N* hydrochloric acids (1.33 : 1) and extracted with diethyl ether. Sulfonated moieties, including the color additive, are discarded in subsequent aqueous extractions of the ether. Carboxylated moieties are removed from the ether by extraction with 2% (w/w) NaOH. The ether is evaporated to near dryness, ethanol (95%) is added, and the solution is analyzed spectrophotometrically in the visible range. The absorbance at each wavelength must not exceed 150% of the absorbance similarly obtained for D&C Red No. 6 Lot AA5169.

Apparatus

(A) Spectrophotometer (Cary 118 or equivalent).

(B) Separatory funnels—one 1000 mL and one 500 mL.

Reagents

Note.—Use *distilled* water when water is required.

(A) Glacial Acetic Acid (ACS grade).

(B) Diethyl ether (Anhydrous)—Note and follow safety precautions on container.

(C) 8 *N* HCl—Pour 165 mL H_2O into a 500 mL graduate. Place the graduate in hood, then add HCl conc. to bring to volume. Carefully pour this solution into a 500 mL Erlenmeyer flask, Stopper and shake. Label the flask.

(D) 2% (w/w) NaOH—Pour ca 190 mL H_2O into a 250 mL mixing graduate. Add 8 g. (5.23 mL) of 50% (w/w) NaOH, bring to 200 mL volume with water, stopper and mix. Pour this solution into a glass bottle, label and stopper with a teflon top.

(E) Ethanol (95%).

Procedure

Weigh a 250 mL beaker to tenths of a mg and add 100 mg of dye. Record weight to tenths of a mg.

Note.—The following work must be performed in the hood.

Add 75 mL of 8 *N* HC1 and 100 mL of glacial acetic acid to the beaker and stir.

Place the beaker on a hot plate and heat with stirring, until all of the dye is in solution.

Remove the beaker from the hot plate, cover with a watch glass and allow to cool to room temperature (1–2 hrs).

When the dye solution is at room temperature, transfer the solution to a 1000 mL separatory funnel.

Rinse the beaker three times with 50 mL portions of H_{20}, transferring each rinse to the 1000 mL funnel.

Add 150 mL of ether to the funnel, stopper and shake for 10 seconds, then invert funnel and open stopcock to remove gas buildup.

Shake the funnel for one minute, opening the stopcock a few times while the funnel in inverted to remove gas buildup. (Use this shake procedure throughout method.)

Allow the funnel to stand until the layers have separated.

Transfer the bottom (aqueous) layer to a 500 mL separatory funnel, add 100 mL of ether, stopper and shake for one minute.

When the layers have separated, drain off the bottom layer into a waste beaker.

Pour the ether layer in the 500 mL separatory funnel into the 1000 mL separatory funnel.

Rinse the 500 mL sep. funnel with 100 mL H_2O, then transfer it to the 1000 mL sep. funnel, stopper and shake for one minute.

When the layers have separated, drain off the bottom aqueous layer into the waste beaker.

Rinse the 500 mL funnel at least three times (total) and repeat the 100 mL water washes until no color is present in the aqueous layer. Discard the bottom aqueous layer to the waste beaker after each separation.

Shake the ether layer twice more with 100 mL portions of H_2O, discarding the bottom aqueous layer after each separation.

Remove the unsulfonated subsidiary color from the ether by shaking the ether layer for one minute with 20 mL of 2% (w/w) NaOH. *Appropriately label* a 100 mL beaker. After the layers separate, drain the aqueous alkaline layer into the beaker and save for the determination of 3-hydroxy-4-[(4-methylphenyl) azo]-2-naphthalenecarboxylic acid, sodium salt.

If there is any color left in the ether, shake for one minute with another 20 mL portion of 2% (w/w) NaHO. After the layers have separated, drain off the aqueous alkaline layer into the 100 mL beaker.

If color remains in the ether layer, repeat the above step for a total of three washes of the ether with 2% (w/w) NaOH. Note: Three washes is usually sufficient to remove the unsulfonated subsidiary.

With the stopper removed, *gently* swirl the ether layer in the sep. funnel twice to separate the remaining aqueous base. Drain this into the 100 mL beaker.

Appropriately label a 250 mL beaker. *Pour* the ether layer into the beaker. Allow the ether to evaporate to *near* dryness. Cool to room temperature. Add ca 8 mL ethanol (95%). Swirl beaker to mix contents. Quantitatively transfer to a 25 mL graduate using ethanol (95%) rinses. Add ethanol (95%) to bring volume to 12 mL.

Spectrophotometer Analysis

Spectrophotometric Parameters:

Scan Range: 400–700 nm
Scan 50 nm/in; 5.0 nm/sec.
Absorbance Range: 0–1 AUFS
Cell length: 1 cm (Note: Reference and Sample cells)

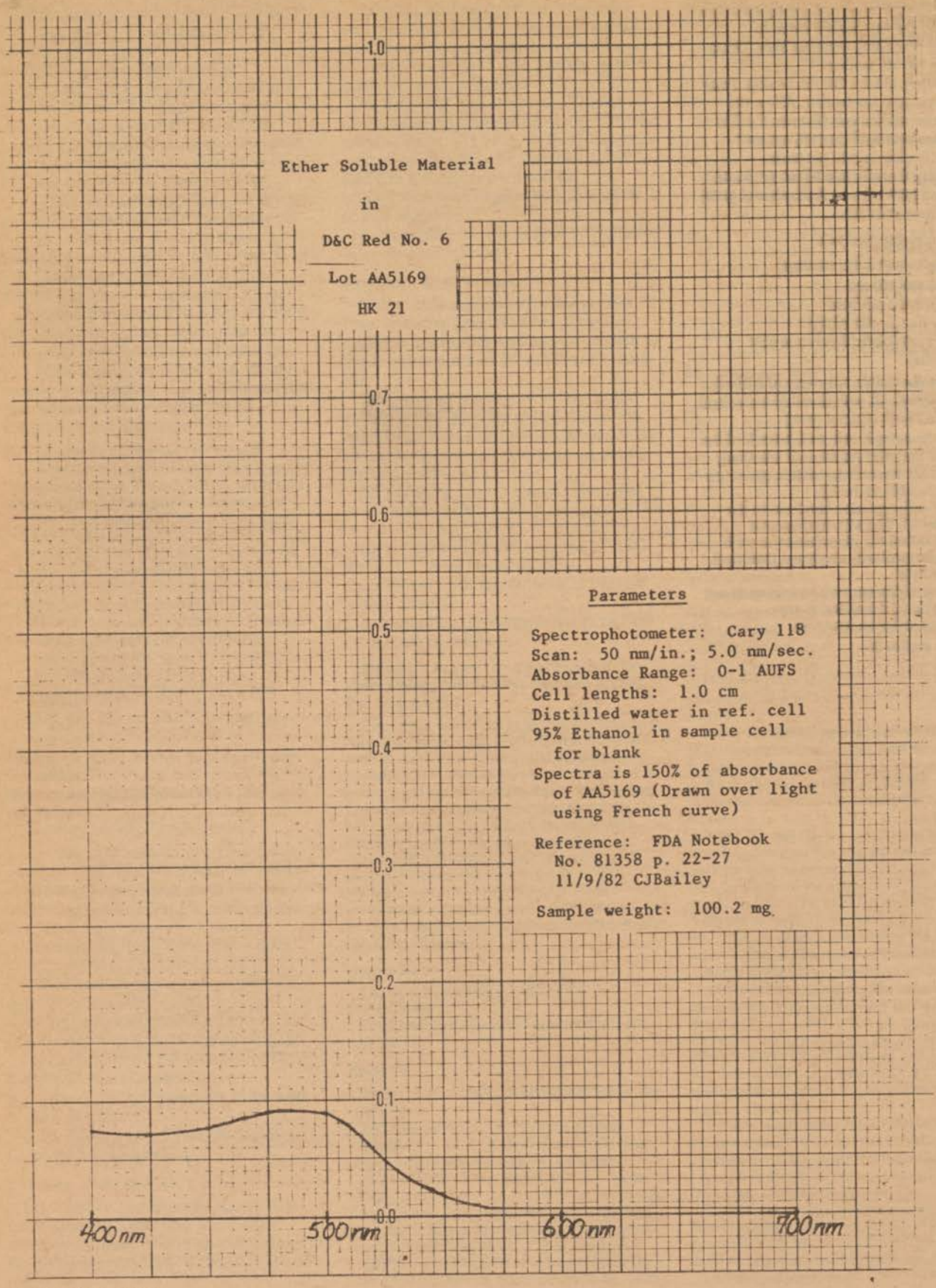
(1) Record the visible spectrum of a blank. Fill the reference cell with distilled water and the sampe cell with ethanol (95%)

(2) Rinse the sample cell with 2–3 mL of the ether soluble material (in ethanol solution); then fill the cell. Record the visible spectrum of the ether soluble material.

(3) Compare the spectra obtained to the spectra attached. The attached spectra represents 150% of the absorbance at each wavelength for similarly analyzed D&C Red No. 6 Lot AA5169.

The spectra of the current sample must not exceed the attached spectra at any wavelength in order to *pass test.*

BILLING CODE 4160-01-M



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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 entries for "D&C Red No. 6" and "D&C Red No. 7."

§ 81.27 [Amended]

b. In § 81.27 *Conditions of provisional listing,* by removing and reserving paragraph (c) and in paragraph (d) by removing the entries for "D&C Red No. 6" and "D&C Red No. 7."

PART 82—LISTING OF CERTIFIED PROVISIONALLY LISTED COLORS AND SPECIFICATIONS

3. Part 82 is amended:

a. By revising § 82.1306, to read as follows:

§ 82.1306 D&C Red No. 6.

(a) The color additive D&C Red No. 6 shall conform in identity and specifications to the requirements of § 74.1306 (a)(1) and (b) of this chapter.

(b) The color additive D&C Red No. 6 may be safely used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 milligrams per daily dose of the drug.

b. By revising § 82.1307, to read as follows:

§ 82.1307 D&C Red No. 7.

(a) The color additive D&C Red No. 7 shall conform in identity and specifications to the requirements of § 74.1307 (a)(1) and (b) of this chapter.

(b) The color additive D&C Red No. 7 may be safely used for coloring drugs such that the combined total of D&C Red No. 6 and D&C Red No. 7 does not exceed 5 milligrams per daily dose of the drug.

Any person who will be adversely affected by the foregoing regulation may at any time on or before January 27, 1983 file with the Dockets Management Branch (address above) written objections thereto. Objections shall show wherein the person filing will be adversely affected by the regulation, specify with particularity the provisions of the regulation deemed 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 issues for the hearing and 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 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.

Effective date. This regulation shall become effective January 28, 1983; 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 pulbication in the **Federal Register**.

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

Dated: December 21, 1982

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc 82-35102 Filed 12-27-82; 8:45 am]

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21 CFR Part 81

[Docket No. 76N-0366]

Provisional Listing of D&C Red No. 6 and D&C Red No. 7; 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 Red No. 6 and D&C Red No. 7 for use as a color additive in drugs and cosmetics. The new closing date will be March 29, 1983. This brief postponement will provide time for the receipt and evaluation of any objections submitted in response to the final regulation (published elsewhere in this issue of the **Federal Register**) approving the petition for the listing of D&C Red No. 6 and D&C Red No. 7 for these uses.

DATES: Effective December 28, 1982, the new closing date for D&C Red No. 6 and D&C Red No. 7 will be March 29, 1983.

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

SUPPLEMENTARY INFORMATION: FDA established the current closing date of December 31, 1982, for the provisional listing of D&C Red No. 6 and D&C Red No. 7 by a rule published in the **Federal Register** of March 27, 1981 (46 FR 18954). The agency extended the closing date until December 31, 1982, to provide time for the completion of chronic toxicity studies and the review and evaluation of these studies by FDA.

After reviewing and evaluating the data, the agency has concluded that D&C Red No. 6 and D&C Red No. 7 are safe for use in drugs and cosmetics. Therefore, elsewhere is this issue of the **Federal Register,** FDA is publishing a regulation that lists D&C Red No. 6 and D&C Red No. 7 for these uses. The regulation set forth below will postpone the December 31, 1982 closing date for the provisional listing of these color additives until March 29, 1983. This postponement will provide sufficient time for receipt and evaluation of comments or objections submitted in response to the regulation that lists D&C Red No. 6 and D&C Red No. 7 for use in drugs and cosmetics.

Because of the shortness of time until the December 31, 1982 closing date, FDA concludes that notice and public procedure on these regulations are impracticable. Moreover, good cause exists for issuing this postponement as a final rule because the agency has concluded that D&C Red No. 6 and D&C Red No. 7 are safe for their intended uses under the Color Additive Amendments of 1960. This regulation will permit the uninterrupted use of this color additive until March 29, 1983. To prevent any interruption in the provisional lising of D&C Red No. 6 and D&C Red No. 7 and in accordance with 5 U.S.C. 553(d) (1) and (3), this regulation is being made effective on December 28, 1982.

List of Subjects in 21 CFR Part 81

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

Therefore, under 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), Part 81 is amended as follows:

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

§ 81.1 [Amended]

1. In § 81.1 *Provisional lists of color additives,* by revising the closing date for "D&C Red No. 6" and "D&C Red No.