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COLOR ADDITIVES

Provisional Regulations; Postponement of Closing Dates

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

[Docket No. 76N-0366]

PART 8—COLOR ADDITIVES

Subpart—Provisional Regulations

POSTPONEMENT OF CLOSING DATES

The Food and Drug Administration (FDA) is postponing the closing dates for the use of 52 provisionally listed color additives. The postponements are conditioned on the undertaking of appropriate scientific investigations and the submission of data to FDA on a prescribed schedule. This order is effective January 31, 1977.

The Commissioner of Food and Drugs proposed, in the FEDERAL REGISTER of September 23, 1976 (41 FR 41860), to postpone the closing dates for the use of certain provisionally listed color additives beyond December 31, 1976, conditioned on the undertaking of appropriate scientific investigations and the submission of data to FDA. The Commissioner proposed to prescribe the required scientific investigations and other procedures for these provisionally listed color additives in new § 8.505 (21 CFR 8.505). The proposal was part of the Commissioner's publicly stated commitment, published in the FEDERAL REGISTER of January 5, 1976 (41 FR 754), to make final determinations about "permanent" listing on as many of the provisionally listed colors as possible and to take steps to resolve finally the status of each of the provisionally listed color additives.

In response to the proposal the Commissioner received 104 comments; they came from consumers, a consumer group, growers and producers of cherries, trade associations, and manufacturers and users of color additives. The comments received and the Commissioner's responses to them are summarized below.

1. Several comments from consumers and a consumer group objected to continued provisional listing of any color additive on the ground that manufacturers and users have had sufficient time since enactment of the Color Additive Amendments of 1960 to establish the safety of all color additives. The comments said that any color additive that has not been proved safe by now should be removed from the provisional list and its use should be prohibited.

The Commissioner advises that various factors have prevented quick decisions about "permanent" listing of certain provisionally listed colors. Three factors—the time needed to do studies on the additives, a legal challenge to FDA authority over cosmetic ingredients, and changing scientific standards for the evaluation of food and color additives—account largely for the delay. These factors are further discussed below.

The regulation below results from the Commissioner's commitment to "close the books" on the provisionally listed color additives. The regulation prescribes both a schedule for the prompt resolution of the status of each provisionally listed color additive and procedures to ensure that the schedule will be followed.

The process of resolving the status of each provisionally listed color additive began with a comprehensive review by FDA scientists of all available data on each provisionally listed color additive. The review was conducted to determine whether the data on any of the provisionally listed color additives supported "permanent" listing, termination of the provisional listing, or requirements to submit additional data. This review led to the termination of the provisional listing for FD&C Red No. 4 and carbon black, by notices published in the FEDERAL REGISTER of September 23, 1976 (41 FR 41852, 41857), and the "permanent" listing of 20 color additives by notices published in the FEDERAL REGISTER between September 23 and November 30, 1976.

The review also led to the conclusion that, while the data did not appear to establish a basis for concern about the safety of the remaining 52 provisionally listed color additives, the available data, evaluated by contemporary standards, do not support "permanent" listing at this time. The regulation prescribes the requirements for testing and a schedule for submission of the results of that testing to FDA and will enable FDA to resolve the status of the remaining provisionally listed color additives. As stated above, three factors largely account for the continuation of the provisional list today. The Commissioner believes that it is important for the public to understand the historical reasons for the continuation of the provisional list.

Congress initially established a closing date for the provisionally listed color additives 2½ years after the effective date of the Color Additive Amendments of 1960 (July 12, 1960). The 2½-year period was chosen based on the expectation that that period would be adequate to conduct the necessary testing on all color additives then in commercial use and, under the terms of the transitional provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86-618, 74 Stat. 404-407 (21 U.S.C. 706 note)), entitled to be provisionally listed. In fact, however, the 2½-year period established by Congress was too brief to permit the completion of necessary scientific investigations, including some chronic animal-feeding studies which run 2 to 3 years, and evaluation of those studies by FDA. Thus, it was almost inevitable that extensions of the closing date for certain of the provisionally listed colors would become necessary even if there had been no change in scientific requirements based upon improvement in scientific testing and evaluation techniques.

When the initial closing dates for the provisionally listed color additives occurred in January 1963, it was necessary to postpone the closing dates. This was because some chronic feeding studies were incomplete and additional chemistry data were required to establish specifications for the provisionally listed color additives. In several instances, postponements were necessary because precise assay methods had not yet been validated. In short, the gaps in the data on these color additives generally did not go to the central question of their safety for human consumption. Although the missing data obviously were needed before final determinations about "permanent listing" could be made by FDA, continued provisional listing for these color additives was consistent with the intent of Congress in providing for the provisional list. Extensions of the provisional list were also granted in a few instances because equivocal results were obtained from chronic feeding studies that required additional long-term study to resolve. This was the case, for example, with FD&C Red No. 4.

A second factor contributing to the several postponements of the closing dates for certain provisionally listed color additives was the unsuccessful efforts of FDA to obtain information about the formulation of all cosmetic products in which color additives were used. These efforts began formally in March of 1966 when former FDA Commissioner James Goddard, M.D., advised the Toilet Goods Association (the predecessor to the Cosmetic, Toiletry, and Fragrance Association) that the so-called "Harvey list" color additives, 21 in number, could not be listed "permanently" without information on the formulations in which the color additives were used. Further consideration of "permanent" listing for the provisionally listed color additives was held in abeyance pending litigation on the issue whether FDA had legal authority to require premarketing clearance of finished cosmetic products. In 1969, the United States Court of Appeals for the Second Circuit held that the provision of the color additive regulations requiring premarketing clearance of finished cosmetic products was not authorized by section 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 376) (*Toilet Goods Association* v. *Finch*, 419 F.2d 21 (2d Cir. 1969)). The Food and Drug Administration did not appeal this decision. Subsequent consideration of the 21 "Harvey list" color additives in light of changed scientific standards for the evaluation of food and color additives resulted in demands for additional data on these and the other provisionally listed colors, and in further postponements of the closing dates for them.

The most important reason for the several postponements of the closing dates for the provisionally listed colors is the dynamics of scientific criteria for the toxicological evaluation of chemical substances. The tools for the safety evaluation of products have greatly improved since 1960. Thus, a color additive first proposed for use today would be studied to determine the potential of the color to induce cancer, effects on reproduction or the fetus, and other types of toxic effects. The scientific techniques for assessing and evaluating these effects are far more sophisticated than those commonly employed in the 1960's. To assure that the

safety of the provisionally listed colors had been evaluated in accordance with contemporary scientific standards before they were listed "permanently," FDA has imposed additional requirements on the sponsors of the additives as significant scientific improvements have occurred. These requirements were imposed as a condition of continued provisional listing. As a result, FDA knows substantially more about the toxicity of most provisionally listed color additives than would be the case had decisions about "permanent" listing been made in the early 1960's.

The scientific investigations and tests prescribed in this regulation conclude a process that has been underway for some time, albeit concededly in a less systematic and vigorous fashion. This process of updating the data on the safety of food ingredients—food additives, substances generally recognized as safe (GRAS), and color additives—as scientific standards for evaluating the safety of such products improves, will continue as long as science remains dynamic.

2. Two comments, one from a consumer and one from a consumer group, asserted that the proposed extension of the provisional list is not authorized by the Federal Food, Drug, and Cosmetic Act and is contrary to the intent of Congress in enacting the Color Additive Amendments of 1960. The comments further implied that the 52 provisionally listed color additives are unsafe.

In paragraph 1 of this preamble, the Commissioner discusses the primary reasons why the provisional list has been extended since 1960. The Commissioner believes that previous extensions were granted for valid reasons and, though Congress probably did not anticipate in 1960 that color additives would be provisionally listed in 1976, further extension of the list is nonetheless consistent with the overriding objective of Congress in enacting the amendments—to have the safety determinations on color additives made on the basis of the best available data.

The implication in the comments that the 52 colors subject to this regulation have not been tested is erroneous. Delays both by sponsors in submitting necessary data to FDA and by FDA in evaluating those data and advising the sponsors of those evaluations have concededly contributed to the necessity for extensions of the provisional list. As indicated in paragraph 1 of this preamble, however, the scientific investigations previously required or required by this regulation as a conditon for continued provisional listing are necessary primarily because of improving scientific standards for evaluating the safety of substances added to food, drugs, and cosmetics. The Commissioner concludes that continued provisional listing for the 52 color additives is consistent with the objectives of Congress in enacting the amendments in 1960 and the agency's responsibilities to protect the public health.

3. One comment contended that the proposal was inadequate because it failed to disclose the empirical data and underlying considerations for the proposed actions, as required by the Administrative Procedure Act, (APA) (5 U.S.C. 553) and the case of "National Welfare Rights Organization v. Mathews," 553 F. 2d 637 (D.C. Cir. 1976). The comment cited as particularly deficient the Commissioner's conclusion that continued use of the 52 provisionally listed colors under the intended conditions of use would not present a hazard to the public health, and the comment asserted that the Commissioner's conclusion, without citing the empirical data and underlying considerations on which it is based, will deprive a court of an adequate administrative record to review the final regulation. Finally, the comment contended that FDA should issue a "more informative" proposal to comply with the requirements of the APA.

The Commissioner has carefully considered the "National Welfare Rights" case cited by the comment, as well as other pertinent legal authority, and concludes that the proposal complies with the requirements of the APA. The preamble to the proposal, the substantial background material, including toxicological reviews of many of the 52 color additives, which were placed on file with the Hearing Clerk, and publication of the proposal in the FEDERAL REGISTER adequately apprised the public of the basis for the proposed action and the underlying facts and considerations that support it. Furthermore, all the safety and functionally data on the 52 color additives have been available to the public under § 8.9(a)(1) (21 CFR 8.9(a)(1)).

The comment contended that the Commissioner's conclusion lacks empirical support and that this prevents intelligent comment or judicial review. The Commissioner's conclusions are based on review of the available data on each of the color additives and the application of standard scientific and toxicological criteria. It obviously is not practicable to reproduce the voluminous safety data on each color additive in the FEDERAL REGISTER, nor would a mere summary of those data enable interested persons to assess the validity of the Commissioner's conclusions. The Commissioner encourages persons who believe that any of the 52 provisionally listed color additives should not be so listed to review the safety data on any such additive and to petition FDA to terminate the provisional listing. Any such petition will receive careful and prompt review.

4. Several comments contended that color additives provide no "benefit" to the public and that their use is purely cosmetic and concluded, therefore, that their use should not be sanctioned by FDA. Other comments opposed the use of any artificial color additives and stated their preference for "natural" foods and food ingredients. One comment cited a recent Gallup poll in which the majority of the persons surveyed favored banning food (and presumably color) additives used only to improve the appearance of food.

A number of comments, on the other hand, supported the use of color additives in food. One comment stated that "We need some color in life. So what if it may be a bit risky. Humanity has lived with these things until this the 20th century." Other comments pointed out that their relatives have eaten colored food for years without suffering adverse effects and suggested letting the consuming public decide if it wants to eat colored foods.

The Commissioner advises that it is Congress that has made the judgment that color additives that have been proved safe should be permitted in food. The role of FDA under the Federal Food, Drug, and Cosmetic Act is not to make the value judgment about whether color additives are "beneficial," but rather to evaluate the data submitted in support of color additive petitions and to approve for use in food, drugs, cosmetics, and devices only those colors that it is reasonably certain are safe. In short, Congress has made the collective judgment that color additives are "beneficial" and should be permitted to be used if proved safe.

The Commissioner recognizes that consumers are not always in a position to decide for themselves if they wish to ingest foods that contain color additives or to distinguish among foods on the basis of the color additives that they contain. Congress, in the Federal Food, Drug, and Cosmetic Act, has permitted most foods to avoid specific labeling of the color additive used. The phrase "artificial color" in the ingredient statement on a food label complies with section 403(k) of the act (21 U.S.C. 343(k)). Thus, a consumer cannot ordinarily determine from a food's labeling which color additives it contains. Additionally, consumers are ordinarily not in a position to determine whether food served in restaurants, institutions, or in someone else's home contains color additives. Thus, it is essential for the protection of consumers that only those colors whose safety is established be permitted in food.

The Commissioner also advises that the absence of observed adverse effects in persons who have consumed food with added color for years cannot be taken as proof of the safety of those colors. Some adverse effects that occur from the ingestion of unsafe chemical substances appear only after many years of exposure. Observable adverse effects occurring immediately after ingestion are unusual. Furthermore, the casual observation of a small group of persons who appear to have suffered no ill effects from consumption of food with added color is not a proper scientific basis for extrapolation to the general population.

Finally, the Commissioner advises that "natural" foods and food ingredients are not necessarily safer than artificial ones. Many natural foods are harmful if ingested in sufficiently large quantities. Additionally, many synthesized ingredients are chemically identical to substances that occur naturally. In short, the notion that all natural foods are safer than all artificial foods is not supported by available scientific data.

5. One comment stated that FD&C Blue No. 1 and FD&C Green No. 3 are carcinogenic and objected to continued provisional listing for these color addi-

tives. In support of this position, the comment referred to pages 106–107 of "Environmental Cancers of the Urinary System" by Dr. Wilhelm C. Heuper. In that book, Dr. Heuper states:

> In view of the occurrence of bladder cancers in producers of widely used paper and food colors (the diphenylmethane dye auramine, and the triphenylmethane dye fuchsin), and of sarcomas of the subcutaneous tissue in rats after their subcutaneous injection (Case et al., 1954; M. H. C. Williams, 1958, 1962; Williams and Bonser, 1962; Walpole, 1963) and the reported occurrence of a bladder cancer in a German producer of Brilliant Blue, another triphenylmethane dye (Bundesministerium für Arbeit, 1957), adequate human and experimental evidence seems to be on hand for reassessing the significance of sarcomas of the subcutaneous tissue induced in rats by several triphenylmethane dyes.

Studies in which a substance is injected subcutaneously into test animals are not ordinarily considered appropriate tests to evaluate the safety of color and food additives. This view has been recognized by the World Health Organization and FDA's Advisory Committee on Protocols for Safety Evaluation (World Health Organization Technical Report Series (Geneva), No. 348, 1967; Toxicology and Applied Pharmacology 20:419, 1971).

Dr. Heuper also refers to a single reported incident of bladder cancer in a worker employed in a facility manufacturing "Brilliant Blue" in Germany. The sole authority for this reference is a 1957 German publication, which was not included with the comment and which is not readily available to FDA. In any event, the isolated report of cancer in an industrial worker dating back to 1957 is not suggestive of a potential for FD&C Blue No. 1 to induce cancer in man when ingested under ordinary conditions of use. The rate and conditions of exposure are different and, as noted, the incident was apparently isolated.

Finally, the chronic feeding studies on FD&C Blue No. 1 and FD&C Green No. 3, although inadequate by contemporary standards, do not suggest that either color may be a carcinogen. Without more substantial data to establish that either color is likely to be carcinogenic, the Commissioner concludes that continued provisional listing for FD&C Blue No. 1 and FD&C Green No. 3 does not present a hazard to the public health. New chronic feeding studies will be conducted on these two color additives under this final regulation as a condition of continued provisional listing. The results of those studies will permit the comment's hypothesis to be tested.

6. One comment objected to the proposed extension of provisional listing for various azo dyes and specifically named FD&C Yellow No. 5 and FD&C Yellow No. 6. Citing a reference from "Occupational and Environmental Cancers of the Urinary System," the comment stated that, according to Dr. Heuper, there is reason to believe that azo dyes contain various carcinogenic amines, including β-naphthylamine.

The Commissioner concurs with the comment's statement that β-naphthylamine is considered to be a carcinogen. Two colors, Ext. D&C Yellow No. 9 and Ext. D&C Yellow No. 10, which were synthesized from β-naphthylamine, were prohibited by FDA from use in drugs and cosmetics because of a finding that they might contain β-naphthylamine. Accordingly, the Commissioner views with concern the possibility that any color additive for food, drug, or cosmetic use might contain the impurity.

β-Naphthylamine is an intermediate that is used in the production of diazotized compounds for industrial use. These compounds are not, however, used in the production of colors intended for use in food, drugs, or cosmetics. β-Naphthylamine is not expected to be present in color additives, therefore, except as a contaminant. The Commissioner is unaware of any data that would indicate that FD&C Yellow No. 5 or FD&C Yellow No. 6 might contain any β-naphthylamine as a contaminant of the finished color or any of the raw materials or as a result of intermediate steps in their production.

However, upon further review of the data on each of the azo dyes, the Commissioner concludes that there are five colors that could possibly contain low levels of β-naphthylamine as impurities—D&C Red No. 10, D&C Red No. 11, D&C Red No. 12, D&C Red No. 13, and D&C Red No. 34. These colors are synthesized from 2-amino-1-naphthalenesulfonic acid which may contain β-naphthylamine.

To resolve the questions raised by this comment, the Commissioner has requested that the petitioners promptly provide to FDA data about the possible contamination of 2-amino-1-naphthalenesulfonic acid and each of the five colors with β-naphthylamine.

Furthermore, in view of the concern that β-naphthylamine may be present in the color additives, FDA has initiated immediate action to investigate the possibility. It will promptly conduct analyses of samples of each of the five colors and 2-amino-1-naphthalenesulfonic acid using very sensitive methods. The Commissioner is continuing the provisional listing for D&C Red No. 10, D&C Red No. 11, D&C Red No. 12, and D&C Red No. 13 because the short period of time required to resolve this question will not present a hazard to the public health. If data become available, either from investigation by FDA or from the petitioners, that indicate that β-naphthylamine may be present in any of the color additives, the Commissioner will take immediate action to protect the public health. The Commissioner advises that FDA is also examining the data on D&C Red No. 34, which was the subject of an order, published in the FEDERAL REGISTER of November 23, 1976 (41 FR 51592), "permanently" listing the color to determine if it might contain β-naphthylamine. The Commissioner will take immediate action to protect the public health if the data indicate that D&C Red No. 34 might contain β-naphthylamine. In the meantime, the Commissioner is staying the order "permanently" listing D&C Red No. 34.

7. Several comments objected to the use in food of any color additive that has not been proved "completely" or "absolutely" safe.

The Commissioner advises that while the objective of "completely" or "absolutely" safe color additives is a worthy one, it is beyond the capability of science to assure complete safety. There is always some risk, however slight, in using in food any substance—natural or artificial, color or other additive. In recognizing this, Congress has provided that FDA must be "reasonably certain" that a food or color additive will be safe when used as intended. Although FDA applies demanding scientific criteria to determine whether color additives are safe, it is not possible to be absolutely certain that consumption of any color additive or other ingredient poses no risk whatever to health.

8. Several comments questioned the basis on which FDA makes judgments about the safety of color additives. A metallurgist conducting research to define the carcinogenic constituents of industrial atmospheres suggested that unneeded alarm is caused by regulatory action taken without substantial experimental evidence. This comment also expressed skepticism about extrapolations made from data derived from tests in animals and applied to man. Another comment suggested that FDA bans substances used in food without justifiable cause and does so merely out of fear that they are carcinogens. The comment noted that test animals are customarily fed very high amounts of the substance being tested.

The Commissioner points out that the testing of substances such as color additives in animals to determine the probable effects of the substance in humans is a longstanding and generally accepted practice, especially for substances such as food and color additives that would ordinarily not be tested in humans. Although extrapolating from animal experience to human risk is an uncertain process, FDA must rely on animal tests as a predictor of the safety of new food ingredients in humans. The Commissioner advises that the test animals are fed seemingly high doses of the test substance to compensate for the lack of sensitivity of tests in relatively small numbers of animals to detect hazards among the much larger human population. Although this technique is not without its difficulties, it is widely employed by the scientific community and is generally accepted as appropriate.

9. A few comments contended that FDA should ban any substance suspected of causing harm.

The Commissioner disagrees. When a safety issue is raised about a compound that FDA previously has approved, the agency must review the question in a reasoned and scientific manner. This approach is rooted in common sense, because it is not difficult to raise questions about the safety of a food substance. If unevaluated questions produced an immediate and uncritical response, the nation's food supply would be in constant chaos, with products

continually being banned and, possibly upon reevaluation, later returned to the grocers' shelves.

10. A few comments suggested that FDA or outside laboratories, rather than the sponsors of color additives, should conduct tests on the provisionally listed color additives. In addition, FDA has received a request from the Cosmetic, Toiletry, and Fragrance Association (CTFA) and the Pharmaceutical Manufacturers Association (PMA) that FDA undertake the testing of 25 provisionally listed drug and cosmetic colors required by the regulation.

The Commissioner concludes that under the Federal Food, Drug, and Cosmetic Act, the primary responsibility for conducting (as distinct from final evaluation) studies to support product applications filed with FDA lies with the sponsors of those applications. Although FDA has, in the past, conducted some studies on color additives, it has not, since passage of the Color Additive Amendments of 1960, assumed the massive responsibility to conduct all such studies. The Commissioner believes that such an undertaking would be an inefficient use of the limited resources of FDA and that other, less costly ways of ensuring the reliability, accuracy, and completeness of submitted data are preferable.

For example, FDA is currently implementing a bioresearch monitoring program designed to audit and upgrade the quality of the studies conducted by testing laboratories and to ensure the basic integrity and reliability of the data submitted to FDA as a result of studies performed in these laboratories. The Commissioner is confident that this far-reaching program will improve the performance of nonclinical laboratories and assure a high level of compliance with the applicable legal and scientific standards. The request of CTFA and PMA and the Commissioner's response thereto are discussed in greater detail elsewhere in this preamble.

11. One comment opposed the use of all colors in foods because of the alleged relationship between ingestion of food and color additives and hyperkinesis in children. The comment called for the labeling of all ingredients used in food.

Behavioral disorders related to the hyperkinetic syndrome are found in children of all socioeconomic groups and in most countries throughout the world. A conservative estimate would be that moderate and severe disorders are found in as many as 3 out of every 100 elementary school children. More males than females appear to be affected. The major symptoms of the disorder are an increase of purposeless physical activity and a significantly impaired span of focused attention. The inability to control physical motion may generate other behavioral consequences. It has been suggested that there are several etiological subgroups within the syndrome.

In 1975, Dr. Ben F. Feingold stated in "Why Your Child is Hyperactive" that artificial colors and flavoring agents produce hyperactive behavioral symptoms in genetically predisposed children. In addition, Dr. Feingold concluded that total withdrawal of the artificial substances through the Feingold Kaiser-Permenente (K-P) diet can be of therapeutic value in the treatment of between 25 and 50 percent of the children with hyperkinesis.

While these reports are anecdotal, the possible relationship between food additives and the hyperkinetic syndrome in children is an important health issue that is currently being studied by various agencies within the Department of Health, Education, and Welfare and by outside groups. One recent study of the Feingold hypothesis was conducted by the Food Research Institute of the University of Wisconsin. The observations and data from this study are currently being collated and evaluated.

The Interagency Collaborative Group on Hyperkinesis (ICGH), composed of scientists from FDA, the National Institutes of Health, the National Institute of Mental Health, and the National Institute of Education, was established in the summer of 1975 to assess all the available data on the possible association between hyperkinesis and diet and to make recommendations for any additional research indicated. Scientists from FDA provided the leadership in organizing the ICGH and in the preparation of the First Report of the Preliminary Findings and Recommendation.

On February 23, 1976, the members of the ICGH prepared and approved three specific research proposals to carry out the recommendation of the report. The studies proposed were as follows:

(1) A Dietary Challenge Study of Artificial Food Colors and Flavors in Children (1 to 5 years old) with Behavioral Disturbances.

(2) A Dietary Challenge Study of Artificial Food Colors and Flavors in School-Age Hyperkinetic Children.

(3) Support to Obtain Data, Results and Interpretation of a Study of Food Additives and Hyperactivity in Children.

The Bureau of Foods, FDA, has provided $37,506 for the funding of study 3, and the National Institutes of Health has provided $106,800 for the funding of a challenge study in children ages 1 to 5 years.

The Commissioner notes further that FDA has consistently supported complete and more informative ingredient labeling of foods. For example, since 1941 FDA has required special dietary foods for infants to include the name of each ingredient, including colors, on the label; and FDA is exploring other ways to achieve complete ingredient labeling. The agency has also supported legislation that would require specific label designation of all colors in food. The Commissioner therefore concurs with the comment on this point and advises that FDA will continue to seek ways to provide more informative food labeling to consumers.

12. The majority of comments were on the action taken by FDA to terminate the provisional listing for FD&C Red No. 4, previously used to color maraschino cherries and short-term ingested drugs. These comments, mainly from cherry growers and industrial users of maraschino cherries, e.g., fruit-cake manufacturers, noted the adverse economic consequences that they assert will result.

The Commissioner advises that the potential adverse economic impact of the decision to terminate the provisional listing of FD&C Red No. 4 was fully considered before FDA acted. Representatives from the National Cherry Growers Association and the Maraschino Cherry and Glace Fruit Association met with FDA officials on several occasions before the action was taken. The Commissioner weighed the possible economic impact of the action but concluded that the Federal Food, Drug, and Cosmetic Act required that priority be given to considerations of public health. The basis for the agency action in terminating the provisional listing is explained fully in the FEDERAL REGISTER of September 23, 1976 (41 FR 41852).

13. One comment from a trade association contended that the available data on the 52 provisionally listed color additives are adequate to support "permanent" listing.

The Commissioner disagrees. These data were recently reviewed in light of contemporary standards by FDA scientists, who concluded that "permanent" listing for the 52 color additives would not be appropriate at this time. The comment offered no data in support of its argument, and it is therefore rejected.

14. The Certified Color Manufacturers Association (CCMA) has advised FDA that it will undertake the chronic feeding studies required under § 8.505(d) of this final regulation on FD&C Blue No. 2, FD&C Green No. 3, and FD&C Yellow No. 6. It has submitted a proposed protocol for these studies, which FDA has reviewed. Subject to a few minor changes, the proposed protocol is satisfactory to FDA.

15. In its comment, CTFA stated that it was reviewing the studies conducted on the D&C color additives and that it would advise FDA shortly of the results of the review. It stated that it would also suggest to FDA "how the body of information on the colors can be supplemented to permit a sound evaluation of their safety."

The Commissioner advises that, in his view, additional studies are required on the D&C colors to assure that they are safe on the basis of current scientific criteria. This does not mean, however, that the provision of additional data from studies already completed might not provide assurance of the safety of the color additives, assuming of course, that the data are derived from studies conducted in accordance with contemporary standards for the evaluation of food and color additives. If adequate additional data are provided on a particular additive, the Commissioner would delete the requirement for studies from the final regulation. The Commissioner emphasizes, however, that the time requirements in § 8.505 will not be altered, unless "extraordinary circumstances" are shown, either to permit submission of data or to allow for evaluation of those

data. The data must, therefore, be submitted to FDA as soon as possible and the requirements of § 8.505 complied with; failure to comply with § 8.505 will result in termination of the provisional listing of the affected color additive.

16. Several comments commended FDA for providing the public the opportunity to comment on the provisionally listed color additives and they generally supported the provisions of the proposal. Other comments supported further testing of food and color additives and the efforts of FDA to require such testing.

17. A number of comments were received from the petitioners for the 52 provisionally listed color additives. Some of the specific comments objected to certain proposed requirements, including the stringent time limitations for completion of studies; others stated that the requirements could be met by the petitioners. A few comments were accompanied by scientific data and literature submitted in support of the comments' assertion that the data on particular color additives were adequate to establish their safety and justify "permanent" listing.

The Cosmetic, Toiletry, and Fragrance Association, one of the petitioners for many of the 52 provisionally listed color additives, advised that the proposed requirements in § 8.505(a) pertaining to eye-area studies were reasonable. It stated that the results of those studies would be submitted to FDA within 45 days of the effective date of this final regulation and that the July 1, 1977 closing date for those color additives was appropriate as long as FDA promptly reviewed the final reports from the eye-area studies.

The Commissioner advises that high priority will be given to the review of the reports of data concerning the provisionally listed color additives. If those reports are received by the dates established in § 8.505 for their submission, FDA will make final determinations about "permanent" listing and issue notices implementing those decisions by the closing dates established in § 8.505. If the reports are not received in timely fashion, the use of the color additive will be terminated immediately.

18. The Certified Color Manufacturers Association commented that proposed § 8.505 appeared "to be written in such a fashion as to require that all co-petitioners agree to perform the steps requisite to satisfying the conditions and that all co-petitioners actually perform the studies." Because all co-petitioners may not share the same interests, the CCMA suggested that § 8.505 be revised to require that at least one petitioner for each color agree to perform, and actually undertake and complete the required studies.

The Commissioner concurs with this suggestion and § 8.505 is revised accordingly.

19. A comment from a trade association stated that adequate specifications for the color additives must be established before beginning any chronic feeding studies. It suggested that the closing dates for any colors that require resolution of chemistry deficiences, in addition to toxicological tests, should be calculated from the date of FDA approval of the chemical and analytical data. A comment from a consumer group contained a parenthetical statement that "it is appalling that for 17 years FDA has explicitly sanctioned the continued use of dyes without even knowing their chemical identity."

The Commissioner advises that, in general, FDA already has adequate knowledge of the identity of each of these colors and has established appropriate specifications. There remain, however, a few issues of identity of minor constituents of some colors that require resolution before the color additives can be listed "permanently."

In the case of graphite, for example, FDA is aware of literature references that indicate that certain types of graphite may contain polynuclear aromatics (PNA's). Because some PNA's are carcinogenic, the petitioner has been requested to supply data capable of demonstrating whether graphite contains PNA's. The Cosmetic, Toiletry, and Fragrance Association has submitted data from the analysis of one batch of graphite that indicated that no PNA's were found using an analytical method with a reported sensitivity of two parts per billion (ppb). The results of this analysis of one batch of graphite from one supplier are however, not adequate to establish the absence of PNA's. Additionally, other unresolved questions related to the analytical method remain. Because, however, there are no definite data that would indicate graphite is likely to contain some amount of PNA's, the Commissioner concludes that its provisional listing may safely continue for the short time necessary to develop and submit the necessary data for graphite.

The remaining eight color additives that require additional chemistry data are subject to certification. These colors are complex chemicals synthesized from various petrochemicals. The purity of the color additives ranges from 85 to 95 percent for the pure color. The remaining 10 to 15 percent is composed almost entirely of water and salts of chlorides and sulfates. In most cases the remaining small fraction of the color not accounted for by one of these substances has also been identified. Because of the complexity of the starting materials and their reactions, however, small amounts of reaction compounds that are not readily identifiable may be formed during synthesis of the color additive. The analytical data are necessary to permit identification of these compounds in color additives and to determine whether they were in the samples of the lots used for toxicological testing.

Pending resolution of these questions, the samples of each of the color additives used in the toxicological tests will be used as templates against which to judge the safety of these minor components. Occasionally, during the certification of a batch of a color, minor amounts of unknown substances are detected. The sample of the color used in the toxicological tests is then analyzed in the same manner to determine whether the unknown is also present. Thus, the toxicological sample serves as a "specification", i.e., a reference standard for judging batches being certified. During the brief period necessary to resolve the chemistry questions for the eight certified colors, the Commissioner concludes that continuation of provisional listing will not present a hazard to the public health.

The Commissioner rejects the suggestion that the closing date for those colors requiring both chemistry data and chronic toxicity data be determined from the submission of the former. Although the Commissioner would agree that the development of specifications of the test material before testing is ordinarily preferable, he does not agree that such an approach is appropriate in this case. The manufacturers of these colors are knowledgeable about their production and purification and will be able to reproduce colors that will comply with specifications developed from the toxicological samples, whether they be from the earlier studies or the new studies that are being required. The manufacturers are in the position to establish the purity of the color used for testing and, thus, its specifications.

20. The Cosmetic, Toiletry, and Fragrance Association questioned the need for a 90-day rabbit dermal study on bismuth oxychloride and submitted additional data to FDA in support of its position. It noted that the material on file with the FDA Hearing Clerk did not include a memorandum discussing the basis for the proposed requirement for the 90-day rabbit dermal study.

The additional data submitted by CTFA have been evaluated and are not adequate to resolve the questions about bismuth oxychloride which generated the proposed requirement. Accordingly, the requirement for a 90-day rabbit dermal study on bismuth oxychloride is retained in the final regulation. Bismuth oxychloride will continue to be provisionally listed pending receipt and evaluation of the studies required under § 8.505.

21. In its comment, Combe, Inc., the petitioner for bismuth citrate, stated that it was prepared to submit a protocol and conduct the short-term (90-day) absorption study in humans, in accordance with proposed § 8.505(b). Combe questioned, however, whether the proposed requirement for a 90-day rabbit dermal study would provide useful data on the safety of bismuth citrate and suggested deletion of the requirement. In support of its request, Combe submitted several articles from scientific journals discussing various aspects of the safety of bismuth citrate.

The Commissioner advises that the petitioner misconceived the purpose of the dermal study. The primary purpose of the study is to determine whether bismuth citrate is toxic when repeatedly applied topically. This study is particularly pertinent in the case of a color additive such as bismuth citrate which is

used in products intended for repeated topical use (hair dyes). The chemistry and analytical data submitted by the petitioner are useful but do not remove the need for the dermal study. The requirements contained in proposed § 8.505 pertaining to bismuth citrate are, therefore, retained in this regulation.

22. The petitioner for caramel questioned the need for subchronic and chronic dermal studies on the color additive. In support of this position, the petitioner referred to a letter received on April 12, 1976, from FDA advising that data for eye-area studies were necessary to permit a final determination to be made. The petitioner stated that the eye-area studies are currently being conducted. The need for dermal studies was questioned because of the absence of a statement to that effect in the letter received on April 12, 1976. The petitioner asked for a reexamination of this requirement.

The available data for caramel have been reexamined, and the Commissioner advises that those data are not adequate to support "permanent" listing of caramel for use in externally applied cosmetics. A 90-day rabbit dermal study and a lifetime mouse skin painting study are therefore necessary for caramel. The Commissioner concludes that the requirements for this color, set forth in § 8.505 (b) and (d) below are appropriate, and continued provisional listing of this color will be based on compliance with the requirements.

23. Three commentors, CTFA, CCMA, and Hilton Davis Chemical Co. asserted that they are not aware of the deficiencies in the chemistry data on the 15 color additives listed in proposed § 8.505(c) and that, without a comprehensive list of those deficiencies, they are unable to comment on this aspect of the proposal.

The petitioners for the 15 colors that require additional chemistry data have been advised repeatedly over the years of the specific deficiencies. The deficiencies were discussed at length in a meeting on January 29, 1976, with representatives of CTFA and Hilton Davis Chemical Co. Letters were sent to each of the petitioners on January 29, 1976, and February 5, 1976, outlining the various deficiencies. Subsequently, the petitioners and their designees submitted data to the Division of Food and Color Additives, Bureau of Foods, indicating that work had been initiated to resolve the various chemistry deficiencies. Meetings were held on March 18, 1976, and May 4, 1976, and at other times, to discuss the progress of this work. A letter was sent to the petitioners, dated May 14, 1976, updating the status of the chemistry data requirements for these 15 color additives. Subsequently, data were submitted for some of the colors. These data were, however, generally received too late for consideration in the drafting of the proposal. The correspondence with the petitioners detailing the chemistry deficiencies and memoranda of the meetings with the petitioners were placed on file with the Hearing Clerk, Food and Drug Administration, when the proposal was published.

The Commissioner concludes that the above-noted actions have provided sufficient notice to the commentors concerning the chemistry deficiencies for the 15 colors. Additionally, a letter has recently been sent to each of the involved petitioners commenting on the data they recently submitted and advising them of any additional data necessary to resolve chemistry deficiencies. Copies of these letters have been placed on file with the Hearing Clerk.

A review of the submitted data by FDA indicates that the data resolve the chemistry deficiencies for a number of colors, specifically: FD&C Yellow No. 6, D&C Red No. 27, D&C Red No. 28, D&C Orange No. 5, and logwood. The requirement for the submission of chemistry data for these five colors and for D&C Orange No. 11, which was inadvertently included in the proposal, is deleted from § 8.505(c) of the final regulation. The remaining 9 color additives—D&C Yellow No. 10, D&C Red No. 6, D&C Red No. 7, D&C Red No. 30, D&C Orange No. 4, D&C Blue No. 6, Ext. D&C Yellow No. 1, Ext. D&C Green No. 1, and graphite—continue to have deficiencies in the chemistry data that require submission of additional data to support their "permanent" listing. The Commissioner concludes that the time requirements in § 8.505 for the submission of these data, as originally proposed, are reasonable and they are retained in the final regulation. Under the regulation, one of the petitioners, or some other interested person through the petitioners, must agree by March 7, 1977, to conduct the necessary studies and must submit the required chemistry data and analytical methods to FDA by August 3, 1977. Continued provisional listing is conditioned upon satisfactory completion of these two requirements.

The closing dates for logwood and graphite have been extended to October 31, 1977, because of the time required to issue final regulations.

The closing dates for the color additives that require chemistry data and new chronic feeding studies have been extended to January 31, 1981.

24. On December 30, 1976, CTFA and PMA filed a request, denominated as a "citizen petition," with FDA under section 706 of the act (21 U.S.C. 376) and § 8.37 (21 CFR 8.37). They requested that FDA conduct the required scientific studies for 25 provisionally listed drug and cosmetic (D&C) color additives. On January 26, 1977, representatives of the associations met with FDA officials to discuss further their request.

The associations contend that FDA can best assure that the testing required by the regulation is done expeditiously and properly if it conducts the studies itself. The request notes that FDA would not be required to conduct all the studies in its own facilities, but could give contracts to independent laboratories to conduct certain studies.

A second aspect of the CTFA–PMA requests relates to the method of financing the required tests. The Commissioner's response to that aspect of the request is discussed later in this paragraph.

The Commissioner rejects the request insofar as it pertains to FDA's undertaking to conduct or arrange for the studies and advises that interested persons, not FDA, must be responsible for conducting the tests required by the regulation. The Commissioner acknowledges that in certain circumstances, which he is not persuaded exist here, it may be appropriate for FDA itself to sponsor toxicological testing on products it regulates. In fact, FDA has, in the past, conducted such studies on certain color additives. In recent years, however, FDA has not simultaneously conducted large numbers of toxicological studies on any compounds. Instead, that responsibility has been left to the proponents of the use of regulated products—in this case the petitioners for the 52 provisionally listed color additives.

The Commissioner believes that in this case the agency's limited resources can best be employed in monitoring the studies and in evaluating the results of those studies. A significantly greater expenditure of agency manpower, not compensable by increasing the certification fee, would be required if FDA were to undertake the responsibility for conducting the studies. Obviously, FDA facilities would be inadequate and arrangements would have to be made with independent laboratories to conduct some, if not all, of the studies. This in itself would require a substantial expenditure of agency resources.

The Commissioner recognizes that CTFA and PMA have offered to cooperate with FDA in ensuring prompt commencement of the studies, including the submission of test protocols, specifications, information, recommendations on independent laboratories, and assistance in monitoring the studies. Nonetheless, the Commissioner concludes that even with such assistance, the resources of FDA that would be required exceed those currently at the Commissioner's disposal.

The Commissioner notes also that there is no legal obligation imposed on FDA to undertake the studies. Although FDA has conducted such studies on occasion and may do so in the future, the Federal Food, Drug, and Cosmetic Act imposes the responsibility for testing on the sponsors of regulated products, not on FDA.

The Commissioner is aware that in recent years, numerous persons have argued that the overall quality, reliability, and integrity of studies conducted to support product applications filed with FDA would improve if FDA or some "disinterested" third party conducted the testing. The agency has expressed skepticism about this suggestion, believing instead that its role should be limited to establishing standards for the conduct of such studies, e.g., good laboratory practice regulations, monitoring the studies while they are in progress (through laboratory inspections), and evaluating the results of those studies. The Commissioner continues to maintain that the advantages of such a program would not justify the burdens on FDA

that would result from a "third party testing" approach.

Finally, the Commissioner notes that at the meeting on January 26, 1977 referred to above, both CTFA and PMA expressed a willingness to undertake the required studies if FDA concluded that it could not or should not assume that responsibility. However, CTFA and PMA also stated that the aspect of their request that relates to the financing of the studies can be considered separately and, in their view, is meritorious.

The two associations note that imposition of a research charge on the certification fee for the 25 provisionally listed color additives covered by their request would fairly distribute the cost of the testing. They point out that the higher certification fee charged to color manufacturers would be passed on directly to the users of color additives in the form of a higher price per pound. The associations also point out that a similar mechanism was used by FDA to finance the studies it conducted on color additives in the 1950's.

The Commissioner agrees that distributing the cost of required testing on regulated products among all who benefit from the products' availability (i.e., all manufacturers and users) is a desirable objective. However, the Commissioner has not fully evaluated the CTFA–PMA request nor have interested persons been afforded the opportunity to comment on the request. Accordingly, the Commissioner concludes that it would be inappropriate to act on the request at this time.

Because, however, the request does appear to have at least theoretical merit, the Commissioner believes that it would be advantageous to obtain the views of interested persons on the financing aspects of the CTFA–PMA request. In particular, the Commissioner solicits comment on the following questions related to the request:

a. Should the request be granted by FDA?

b. If so, how should the cost of conducting the studies be distributed? Specifically, should the same research charge be added to the certification fee for each color or should each color additives being tested "pay its own way"?

The views of interested persons on these questions and all other aspects of the request are solicited. To permit a prompt resolution of this matter, those views should be submitted to the Hearing Clerk, FDA, by March 7, 1977.

25. Three comments, all from trade associations, contended that the proposed closing date of December 31, 1980, for those provisionally listed color additives that require new chronic feeding studies was unrealistic. The comments questioned whether the petitioners or FDA could meet that deadline. The comments noted the possibility of unavoidable delays and difficulty in locating testing facilities and qualified personnel to conduct the studies. One comment stated that 42 months was not sufficient to conduct and evaluate the results of the studies and noted that "the FDA's proposed deadlines could be met only if all the necessary steps were accomplished without any unforeseen problems arising and with the imposition of an undue amount of pressure on the responsible parties." A closing date of June 30, 1981, was suggested by one of the comments.

The Commissioner concludes that the comments have not established that the December 31, 1980 closing date is unreasonable or unrealistic. The Commissioner agrees with the comments insofar as they recognize that conscientious, concerted, and forceful action will be necessary to meet the deadlines imposed by the final regulation. This was the Commissioner's intent in proposing the strict schedule in § 8.505. The Commissioner notes also that the strict schedule is applicable to both the petitioners and FDA. The period allotted for FDA to review the data and to make final determinations about "permanent" listing is very short and will require that the highest priority be attached to completion of that effort. The Commissioner believes that it is reasonable to expect that the same high priority will be given to this project by the petitioners. Final determinations on the provisionally listed colors can be made in a timely fashion only if demanding but realistic time requirements are imposed.

In the unlikely event that unforeseen and unavoidable circumstances arise to make compliance with the requirements of the final regulation virtually impossible, the Commissioner will consider requests for brief extensions of the closing dates. The Commissioner cautions, however, that such requests will be considered only if "extraordinary circumstances" exist and maximum effort has been given to meeting the deadlines.

The closing dates of July 1, 1977, September 30, 1977, and December 31, 1980, were proposed in § 8.505 (a), (b), (c), and (d) respectively, based on the Commissioner's expectation that the final regulation would be issued by December 31, 1976. Because of the unexpectedly lengthy time required to review the comments and the resulting delay in issuing this regulation, the closing dates established in § 8.505 (b), (c), and (d) have been extended for an additional 30 days. Thus, the closing dates in § 8.505 (b) and (c) will be October 31, 1977, and the closing dates in § 8.505(d) will be January 31, 1981. The closing date for the provisionally listed color additives that require eye-area studies under § 8.505(a) is retained at July 1, 1977, because those studies are underway and the petitioners have advised FDA that they can meet the proposed deadlines. Finally, all the deadlines imposed by § 8.505 have been computed from the date of publication of the final regulation in the FEDERAL REGISTER.

26. A requirement that progress reports be submitted to FDA on the chronic feeding studies required by § 8.505(d) was inadvertently omitted from the proposal. Section 8.505(d)(3) has been revised to require the submission to FDA of an initial progress report and further reports at 6-month intervals thereafter.

Having evaluated the comments and the data submitted with them, the Commissioner concludes that the extension of the closing dates for the provisionally listed color additives listed in § 8.501 subject to the conditions of § 8.505 is reasonable and in the public interest.

In accordance with the provisions of 5 U.S.C. 553 (d)(1) and (d)(3) this postponement is effective on January 31, 1977 so as to permit the uninterrupted use of the affected color additives.

Therefore, under the transitional provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86–618, 74 Stat. 404–407 (21 U.S.C. 376 note)) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)) Part 8 of Subchapter A of Title 21 of the Code of Federal Regulations is amended as follows:

1. By amending § 8.501 by revising the introductory text and the tables in paragraphs (a), (b), (c), (f) and (g) to read as follows:

§ 8.501 Provisional lists of color additives.

The Commissioner of Food and Drugs finds that the following lists of color additives are provisionally listed under section 203(b) of the Color Additive Amendments of 1960 (sec. 203(b), 74 Stat. 405 (21 U.S.C. 376 note)). Except for color additives for which petitions have been filed, progress reports are required by January 1, 1968, and at 6-month intervals thereafter. Specifications for color additives listed in paragraphs (a), (b), and (c) of this section appear in the respective designated sections. The listing of color additives in this section is not to be construed as a listing for surgical suture use unless color additive petitions have been submitted for such use or the Commissioner has been notified of studies underway to establish the safety of the color additive for such use. The color additives listed in paragraphs (a), (b), and (c) of this section may not be used in products which are intended to be used in the area of the eye. The color additives listed in paragraphs (a), (b), (c), (f), and (g) of this section are provisionally listed until the closing dates set forth therein, conditioned on compliance with the applicable requirements of paragraphs (a), (b), (c), and (d) of § 8.505.

(a) • • •

	Closing date		Restrictions
	Food use	Drug and cosmetic use	
FD&C Green No. 3 (§ 9.23 of this chapter)	Jan. 31, 1961	Jan. 31, 1961	
FD&C Yellow No. 5 (§ 8.275 of this chapter)	do.[1]	do.	
FD&C Yellow No. 6 (§ 9.41 of this chapter)	do.	do.	
FD&C Red No. 3 (§ 8.242 of this chapter)	do.[1]	do.	
FD&C Blue No. 1 (§ 8.206 of this chapter)	do.[1]	do.	
FD&C Blue No. 2 (§ 8.4022 of this chapter)	do.	do.	Food and ingested drugs.
Lakes (FD&C) (§ 9.100 of this chapter)			

[1] Lakes only.

(b) * * *

	Closing date	Restrictions
D&C Green No. 5 (sec. 8.4069 of this chapter)	Jan. 31, 1961	
D&C Green No. 6 (sec. 8.4070 (a) and (b) of this chapter)	do.	
D&C Yellow No. 10 (sec. 9.133 of this chapter)	do.	
D&C Red No. 6 (sec. 9.151 of this chapter)	do.	
D&C Red No. 7 (sec. 9.152 of this chapter)	do.	
D&C Red No. 8 (sec 9.153 of this chapter)	do.	Sec. 8.503.
D&C Red No. 9 (sec. 9.154 of this chapter)	do.	Do.
D&C Red No. 10 (sec. 9.155 of this chapter)	do.	Do.
D&C Red No. 11 (sec. 9.156 of this chapter)	do.	Do.
D&C Red No. 12 (sec. 9.157 of this chapter)	do.	Do.
D&C Red No. 13 (sec. 9.158 of this chapter)	do.	Do.
D&C Red No. 19 (sec. 9.164 of this chapter)	do.	Do.
D&C Red No. 21 (sec. 9.166 of this chapter)	do.	
D&C Red No. 22 (sec. 9.167 of this chapter)	do.	
D&C Red No. 27 (sec. 9.172 of this chapter)	Jan. 31, 1961	
D&C Red No. 28 (sec. 9.173 of this chapter)	do.	
D&C Red No. 30 (sec. 9.175 of this chapter)	do.	
D&C Red No. 33 (sec. 9.178 of this chapter)	do.	Sec. 8.503.
D&C Red No. 36 (sec. 9.181 of this chapter)	do.	Do.
D&C Red No. 37 (sec. 9.182 of this chapter)	do.	Do.
D&C Orange No. 4 (sec. 9.201 of this chapter)	Oct. 31, 1977	External use only.
D&C Orange No. 5 (sec. 9.202 of this chapter)	Jan. 31, 1961	Sec. 8.503.
D&C Orange No. 10 (sec. 9.207 of this chapter)	do.	
D&C Orange No. 11 (sec. 9.208 of this chapter)	do.	
D&C Orange No. 17 (sec. 9.214 of this chapter)	do.	Do.
D&C Blue No. 6 (sec. 9.242 of this chapter)	do.	
Lakes (D&C) (sec. 9.280 of this chapter)		

(c) * * *

	Closing date	Restrictions
Ext. D&C Yellow No. 1 (sec. 9.301 of this chapter)	Oct. 31, 1977	
Ext. D&C Green No. 1 (sec. 9.400 of this chapter)	do.	
Lakes (ext. D&C) (sec. 9.440 of this chapter)		

(f) * * *

	Closing date	Restrictions
Logwood	Oct. 31, 1977	Surgical suture use only.

(g) * * *

Color additive	Closing date	Restrictions
Aluminum powder	July 1, 1977	None.
Annatto	do.	Do.
Bismuth citrate	Oct. 31, 1977	For use as a color component in hair dye.
Bismuth oxychloride	do.	None.
Bronze powder	July 1, 1977	Do.
Caramel	Jan. 31, 1961	Do.
Carmine	July 1, 1977	Do.
Carotene	do.	Do.
Chromium hydroxide green	do.	Do.
Chromium oxide greens	do.	Do.
Copper, metallic powder	do.	Do.
Ferric ferrocyanide (iron blue)	do.	Do.
Graphite	Oct. 31, 1977	Do.
Guanine (pearl essence)	July 1, 1977	Do.
Lead acetate	Oct. 31, 1977	For use as a color component in hair dye.
Mica	July 1, 1977	None
Zinc oxide	do.	Do.

2. By adding new § 8.505 to read as follows:

§ 8.505 Conditions of provisional listing.

The closing dates for the use of the color additives provisionally listed in § 8.501 are postponed until the dates established in that section conditioned on compliance with the requirements of paragraphs (a), (b), (c), and (d) of this section, where applicable. The closing dates will not be postponed beyond the dates in § 8.501 unless extraordinary circumstances are shown. Requests for further postponement based on extraordinary circumstances shall be submitted in writing and state in detail the basis for the request. If the requirements of paragraphs (a), (b), (c), and (d) of this section are not complied with, the provisional listing for the color additive(s) involved will be terminated immediately.

(a) The closing date for the following 14 color additives is postponed until July 1, 1977, while 4-week eye area studies in the rabbit are conducted and evaluated, and subject to compliance with the requirements of this paragraph: Aluminum powder, annatto, bismuth oxychloride, bronze powder, caramel, carmine, carotene, chromium hydroxide green, chromium oxide greens, copper (metallic powder), ferric ferrocyanide, guanine (pearl essence), mica, and zinc oxide.

(1) At least one petitioner for each of the 14 color additives listed in paragraph (a) of this section shall agree in writing by March 7, 1977 to undertake the eye area studies.

(2) A full written report of the results of the studies shall be submitted to the Division of Food and Color Additives, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, by March 21, 1977.

(3) The petitioners undertaking the studies shall immediately notify the Division of Food and Color Additives of any findings that indicate a potential for the color additive to cause adverse effects.

(b) The closing date for bismuth citrate, bismuth oxychloride, caramel, and lead acetate is postponed until October 31, 1977, while short-term studies are conducted and evaluated, and subject to compliance with the requirements of this paragraph.

(1) At least one petitioner for each of of the four color additives listed in paragraph (b) of this section shall agree in writing by March 7, 1977 to undertake the short-term studies on the color additives.

(2) A full written report on the absorption studies for bismuth citrate and lead acetate and a full written report on the subchronic studies for bismuth citrate, bismuth oxychloride, and caramel shall be submitted to the Division of Food and Color Additives, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, by August 3, 1977.

(3) The petitioners undertaking the studies shall immediately notify the Division of Food and Color Additives of any findings that indicate a potential for the color additive to cause adverse effects.

(c) The closing date for the following nine color additives is postponed until October 31, 1977, while chemistry data and analytical methods to establish specifications for them are developed and evaluated and subject to compliance with the requirements of this paragraph: D&C Yellow No. 10, D&C Red No. 6, D&C Red No. 7, D&C Red No. 30, D&C Orange No. 4, D&C Blue No. 6, Ext. D&C Yellow No. 1, Ext. D&C Green No. 1, and graphite.

(1) At least one petitioner for each of the nine color additives listed in paragraph (c) of this section shall agree in writing by March 3, 1977 to undertake to develop the necessary chemistry data and analytical methods for the color additives.

(2) The required chemistry data and analytical methods shall be submitted to the Division of Food and Color Additives, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, by August 3, 1977.

(3) The petitioners undertaking the studies shall immediately notify the Division of Food and Color Additives of any findings that indicate a potential for the color additive to cause adverse effects.

(d) The closing date for the following 32 color additives is postponed until January 31, 1981, while chronic toxicity feeding studies and in the case of caramel, a lifetime mouse skin painting study, are conducted and evaluated, and subject to compliance with the requirements of this paragraph: FD&C Yellow No. 5, FD&C Yellow No. 6, D&C Yellow No. 10, FD&C Red No. 3, D&C Red No. 6, D&C Red No. 7, D&C Red No. 8, D&C Red No. 9, D&C Red No. 10, D&C Red No. 11, D&C Red No. 12, D&C Red No. 13, D&C Red No. 19, D&C Red No. 21, D&C Red No. 22, D&C Red No. 27, D&C Red No. 28, D&C Red No. 30, D&C Red No. 33, D&C Red No. 36, D&C Red No. 37, FD&C Green No. 3, D&C Green No. 5, D&C Green No. 6, FD&C Blue No. 1, FD&C Blue No. 2, D&C Blue No. 6, D&C Orange No. 5, D&C Orange No. 10, D&C Orange No. 11, D&C Orange No. 17, and caramel.

(1) At least one petitioner for each of the 32 color additives listed in paragraph (d) of this section shall agree in writing by March 7, 1977 to undertake the required studies on the color additives.

(2) The petitioners undertaking the studies shall submit a protocol for the conduct of the studies to the Division of Food and Color Additives, Food and Drug Administration, 200 C St. SW., Washington, DC 20204, for review, and acceptance or rejection, by April 5, 1977.

(3) An initial progress report of the studies on the color additives shall be submitted to the Division of Food and Color Additives by December 31, 1977. Further progress reports shall be submitted at 6-month intervals thereafter. A full report of the studies conducted on the color additives shall be submitted to the Division of Food and Color Additives by August 4, 1980.

(4) The petitioners undertaking the studies shall immediately notify the Division of Food and Color Additives of any findings that indicate potential for the color additive to cause adverse effects.

Effective date: This regulation shall be effective January 31, 1977.

(Title II, Pub. L. 86-618, 74 Stat. 404-407 (21 U.S.C. 376 note).)

Dated: January 31, 1977.

JOSEPH P. HILE,
Acting Commissioner of Food and Drugs.

[FR Doc.77-3362 Filed 1-31-77;12:08 pm]