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PART V:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

■

HUMAN DRUG AND COSMETIC PRODUCTS

Chloroform as an Ingredient

Title 21—Food and Drugs

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

SUBCHAPTER D—DRUGS FOR HUMAN USE

SUBCHAPTER G—COSMETICS

[Docket No. 76N-0091]

PART 310—NEW DRUGS

PART 700—GENERAL

Chloroform as an Ingredient of Human Drug and Cosmetic Products

The Food and Drug Administration (FDA) is issuing final regulations declaring that any human drug product containing chloroform as an ingredient (active or inactive) is a new drug and is misbranded, and any cosmetic product containing chloroform as an ingredient is adulterated. These final regulations are effective July 29, 1976. Therefore, after July 29, 1976, any human drug or cosmetic product containing chloroform that is introduced or delivered for introduction into interstate commerce will be subject to regulatory action.

These regulations are based on a notice published in the FEDERAL REGISTER of April 9, 1976 (41 FR 15026) in which the Commissioner of Food and Drugs proposed to prohibit the continued use of chloroform as an ingredient of human drug and cosmetic products. Interested persons were invited to submit comments on the proposal on or before May 10, 1976.

The final regulations are essentially the same as those proposed, and require any holder of an approved new drug application (NDA), or any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND), for a drug product containing chloroform as an ingredient, to submit a supplemental application or amend his IND to provide for a revised formulation removing chloroform as an ingredient. If a drug product now contains more than 1 percent chloroform, the revised formulation containing no chloroform may not be marketed before the receipt of written notice of approval of the supplemental application by FDA. If a drug product now contains 1 percent or less chloroform, the revised formulation containing no chloroform may be marketed after submission of a supplemental application but prior to the receipt of written notice of its approval by FDA. Failure to submit a supplemental application or to amend an IND notice in accordance with this regulation would be grounds for withdrawal of approval of an application or termination of an IND notice.

As stated in the preamble to the proposal, reformulation to remove chloroform from a drug product that is not now subject to requirements for an approved NDA may occur without prior agency approval regardless of chloroform content. Reformulation of such products may in some cases, as where the percent of chloroform content is significant, affect the product's present legal status under the Federal Food, Drug, and Cosmetic Act. Inquiries concerning the new drug status of any reformulation may be directed in writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD-310), 5600 Fishers Lane, Rockville, MD 20852.

The Commissioner advises that reformulation of a human drug product to remove chloroform as an active or inactive ingredient constitutes a "material change" as defined in § 207.3(g) (21 CFR 207.3(g)) requiring the assignment of a new National Drug Code (NDC) number in accordance with § 207.35(b)(4) (21 CFR 207.35(b)(4)). Section 207.35(b)(4) requires that a new NDC number shall be assigned whenever any material change occurs in product characteristics. The term "any material change" is defined in § 207.3(g) to include, among other things, any change in the quantity or identity of the active ingredients, any significant change in the labeling of a prescription drug, and any significant change in the label of an OTC drug. Therefore, since section 502(e)(1)(A)(ii) of the act (21 U.S.C. 352(e)(1)(A)(ii) requires that the label of all chloroform-containing drug products bear the quantity or proportion of chloroform, whether active or inactive, the removal of chloroform from the formulation of such a product would necessitate a change in the label. Further, removal of chloroform from a formulation as an active ingredient would affect a product's characteristics. It is therefore clear that reformulation of a chloroform-containing drug product to remove chloroform meets the definition of "any material change" in § 207.3(g) thereby requiring a new NDC number in accordance with § 207.35(b)(4).

In response to the proposal, comments were received from manufacturers, a physician, a State consumer affairs unit, a professional association, trade associations, and individuals. Several comments contained specific requests for revisions or clarification of the regulation. A summary of the significant comments and the Commissioner's conclusions are as follows:

1. One comment from the Cosmetic, Toiletry and Fragrance Association, Inc. (CTFA), which also submitted safety data to FDA on studies involving the use of chloroform, questions the relevancy, design, execution, and interpretation of the National Cancer Institute (NCI) studies, and expressed the opinion that it is scientifically unjustified to disregard CTFA's studies in favor of the NCI studies. The specific points raised by the comment in opposing the Commissioner's determination that chloroform is a carcinogen or is otherwise a deleterious substance are as follows:

a. The comment contends that the NCI studies in no way consider the differences in metabolism between rodents and man. In support of this contention regarding differences in metabolism, the comment cities an article by Hill et al., "Genetic Control of Chloroform Toxicity in Mice," *Science*, 190:159, 1975; a recent review by Charlesworth in *BIBRA* (British Industrial Biological Research Association) *Information Bulletin*, 14:225, 1975, which cites Taylor et al. in *Xenobiotica*, 4:165, 1974; and a paper entitled "Covalent Binding of Haloalkanes to Liver Constituents, but Absence of Mutagenicity on Bacteria in a Metabolizing Test System" by Uehleke, Greim, Kramer and Werner, presented at the fifth meeting of the European Environmental Mutagen Society, Florence, October 19–22, 1975. The comment states that (1) Hill et al. demonstrated that there are genetic factors in mice that affect susceptibility to chloroform lethality and induction of organ pathology and that these are associated with a metabolite whose formation is regulated by genetic factors; (2) Charlesworth reported distinct species differences to show that the metabolic fate of chloroform in mice, and most likely in rats, is not the same as in man, that there are sex-linked differences in metabolism that are peculiar to the mouse, and that man appears to eliminate more of the chloroform unchanged in the exhaled air; (3) Taylor et al. concluded that the mouse is an unsuitable species for evaluating the toxic effects of chloroform; and (4) Uehleke found in the "Ames study" that chloroform is not mutagenic and unlikely to be carcinogenic.

The comment further states that a "recognized international expert in oncology" concluded that, in consideration of the findings in the NCI report and those obtained by himself, "there is obviously wide species, strain, and sex variation both in the incidence of spontaneous tumor of the liver and kidney and in the response of these organs to chloroform." The comment claims that such a conclusion is supported by an opinion expressed by Dr. Grasso in a talk entitled "Evaluation of the Hepatoma in the Rodent in Carcinogenesis Bioassay" summarized in *BIBRA*, 1975 ("The Value of the Mouse in Carcinogenicity Testing"), in which he stated that there is considerable disagreement on the diagnosis of hepatic nodular lesions.

The Commissioner views the conclusions expressed in the comment as relying on the finding that, in studies of three mouse strains, male and female mice showed a sex-linked difference in ability to metabolize choloroform. The Commissioner does not agree that this forms an adequate basis for rejecting the mouse as a useful experimental animal, especially since the work of Hill et al. indicates that this variability exists not only between sexes but also within the same sex among different strains of the same species. Since these authors cite findings in humans of large interindividual differences in the disposition of commonly used drugs—differences which they attribute to genetic variability—it is not surprising that chloroform toxicity would be variable in the same species as well.

The Commissioner points out that the NCI report observes the variation in species and sex in the incidence of spontaneous tumor of the liver and kidney, and the response of these organs to chloroform. The report notes that the Osborne-Mendel strain was selected by

NCI because it was reported to be sensitive to the carcinogenic effects of carbon tetrachloride (CCl_4). The question of genetic drift within a strain might also be a factor since the positive control (CCl_4) produced a relatively low response (<5 percent with hepatocellular carcinomas). Thus, if anything, the Osborne-Mendel rats used in the NCI studies appear to be less sensitive to the heptaocarcinogen than those reported in the literature.

The Commissioner recognizes that there is disagreement among pathologists on diagnosis of lesions, including hepatic nodular lesions. However, proliferative changes and neoplastic lesions are discussed in considerable detail on pages 32–37 and 40 of the NCI report. The critique submitted by the comment provides no new information that would negate the effects discussed in the pathology section of the NCI report.

Regarding the reported findings of Uehleke in the "Ames study," which used a bacterial system, the Commissioner recognizes that rapid progress is being made in the development of mutagenicity test systems. He is aware of a number of reports indicating a mutagenicity-carcinogenicity correlation using these test systems. However, a number of "false positives" as well as "false negatives" have been observed in these test systems. Such tests using nonmammalian systems have not been validated for establishing correlations and are not considered an appropriate basis for regulatory actions.

b. The comment also argues that the dosage in the NCI studies was excessive and thus does not support the contention of risk to humans. Noting that the NCI report states that the methodology used in their studies differs from that which is currently used by NCI, the comment states that the most serious defects in the methodology used are the inadequacy of the subchronic toxicity study to determine the maximal tolerated dose (MTD) and one-half MTD, and the failure to employ a meaningful definition of MTD. The comment further states that had a proper and reliable subchronic study been conducted, employing liver and renal function measurements as well as histological assessment of the effects of chloroform upon the liver and kidney, it would have been found that the dose levels used were too toxic. In support, the comment notes that in the NCI rat study, the dose levels had to be reduced after 22 weeks of treatment because the lethal consequences were too great. The comment also cites in support a short term study conducted at Bio/dynamics Inc. at dosage levels of 60, 120, 240, and 480 milligrams/kilogram and with the same strain of mice as that used in the NCI study. In the Bio/dynamics Inc. study both males and females had poor tolerance to the chloroform and at the 480 and 240 milligrams/kilogram levels most of the mice died.

It is the Commissioner's opinion that the growth and survival curves as plotted for the mice in the NCI report reveal no significant effect on growth from the dosages administered, and only in the high-dose-level female mice is there an effect seen on survival. However, this effect was observed late in the study, when the death rate showed a sudden increase after the 70th week. The Commissioner therefore concludes that the dosages in the NCI mouse study conform to the standards generally accepted for an MTD to be used in carcinogenicity studies.

In the NCI rat study, it is true that the survival rate for chloroform-treated rats was lower than that for control rats. However, in the Commissioner's view the high dosage level for male rats appears to conform to standards for MTD when the first 90 days of the growth curves are examined. The comment's objection regarding excessive dosage (> MTD) would apply only to female rats. In this regard the Commissioner notes that the statement in the comment that dosage levels employed had to be reduced after 22 weeks because of lethality applies only to the female rats. Despite the reduction in dosage, the survival curves show a consistently lower survival rate. However, the Commissioner emphasizes that there was no increase in tumors reported for these animals. Rather, it was only in the male rats that an increased incidence of renal tumors was reported.

The comment also points out that the ratio of tumor-bearing animals to animals involved in all chloroform treatment groups is less than that found in both male and female matched control groups. This observation, however, is noted and described by NCI in their report as not significant. Moreover, the Commissioner believes the distribution of other than kidney tumors to be normal. Aside from this, the comment disregards the dose-related time of tumor onset. The CTRA analysis further states that "• • • data for the female groups indicate that chloroform treatment may have actually exerted beneficial effects." Obviously, the lethal effects cannot be viewed as beneficial. Finally, the Commissioner notes that in the case of male rats, where dosage would appear to conform to the generally accepted standards for carcinogenicity studies, definite evidence of kidney carcinogenicity appeared.

It is the Commissioner's view that the study conducted by Bio/dynamics Inc. was one of expediency and that the report was hastily prepared. The report indicates that the animals used were not of comparable age and weight as those used in the NCI study, there are apparent inconsistencies in some of the data tables, and the supplier of the mice for the Bio/dynamics Inc. study was different from that for the NCI study. The health of the mice is also questionable. Through communications with NCI, the Commissioner has been advised that the colony of mice of the supplier of Bio/dynamics Inc. showed pinworm infestations and high hepatitis virus titers. The CTFA representative was advised of this problem before its study was performed. In addition, the period of adaptation and quarantine appears to be inadequate since the mice were shipped 5 days prior to the administration of chloroform.

In response to the reported intolerance and the high mortality rate reported by the Bio/dynamics Inc. study, the NCI investigators administered dosages of 100, 200, 300, and 400 milligrams/kilogram of chloroform to groups of mice for 14 days. No deaths were observed for any group during this period. To produce lethality, dosages of 3620 and 5000 milligrams/kilogram were administered to these animals. Thus, except as stated above, the Commissioner cannot explain the results of the Bio/dynamics Inc. study. However, he recognizes that disparities in results may be due to variations in environmental, technical, and other experimental factors.

c. The comment also questions the bases for selecting the colony controls in the NCI study. It expresses the opinion that the NCI conducted the study with insufficient controls, citing the chloroform-matched colony group as an example, and then stacked the numbers by culling controls from other studies. The comment states that the so-called controls were not housed in the same room nor were they put on the study simultaneously with the treated and matched colony groups. Further, it cites as objectionable that animals that received other volatile agents, among which was carbon tetrachloride, were housed in the same room with the animals receiving chloroform.

The NCI report recognizes that the number of matched controls was less than that used in its current bioassay program. Despite this limitation, the induction of hepatocellular carcinoma in mice was highly significant, and the report concludes that this bioassay was a valid test for carcinogenic effect. The Commissioner rejects the charge of "culling" or "stacking." The NCI study incorporated colony controls of the same strain and source, maintained in the same room and in the same manner as the chloroform "matched" controls in the mouse-study analysis. The influence of other chemicals being tested in the same room is discussed extensively in the NCI report, on pages 41–43. These limitations were recognized and considered; in the Commissioner's view, they do not call into question the results of the NCI study.

d. The comment argues that the extraordinarily high doses of chloroform used in the NCI study may show that hepatocellular carcinoma in mice was secondary to the liver-necrotizing effect of chloroform. The comment points to FDA action on selenium published in the FEDERAL REGISTER of April 27, 1973 (38 FR 10458) and January 8, 1974 (39 FR 1355) and states that selenium was determined not to be a carcinogen for this very reason.

The Commissioner advises that he is not aware of any data supporting the secondary carcinogenesis argument regarding chloroform forwarded by the comment, nor do any data submitted to FDA by CTFA support such an argument. Further, experts in the field of liver car-

cinogenesis today do not regard necrosis as sufficient cause for tumor induction.

e. The comment contends that FDA has never made a determination that a substance is carcinogenic on the basis of a single unreplicated study where there are contradictory data, and it refers to saccharin, where the studies produced conflicting test results, as an example.

The Commissioner advises that the reference to saccharin is neither analogous nor applicable to the chloroform toxicity and carcinogenicity bioassays relied upon in this action. Thus far, the results of studies using saccharin have been inconclusive; additional studies are ongoing. The results of the NCI studies are conclusive. In addition, the studies submitted by CTFA were conducted at lower dosages than those reported by NCI. The lack of sensitivity of the current carcinogenesis bioassays in rodents is well recognized. Thus the positive finding with chloroform should be given greater weight than studies at lower dosages using small numbers of animals.

f. The comment noted that the proposed action had not been referred to the Toxicology Advisory Committee. The comment cited § 2.322 (21 CFR 2.322) of the proposed regulations on FDA administrative practices and procedures published in the FEDERAL REGISTER of September 3, 1975 (40 FR 40682) that states that issues involving a determination of carcinogenicity under section 409(c)(3)(A), 512(d)(1)(H), or 706(b)(5)(B) of the act will ordinarily be referred to the Toxicology Advisory Committee. The comment expressed the belief that its scientific critique of the NCI studies demonstrates compelling reasons why the matter should now be referred to the Toxicology Advisory Committee before final action is taken.

The Commissioner rejects this comment. Technically, this action does not fall under the statutory sections cited in proposed § 2.322. More importantly, the NCI report was reviewed by a panel of consultants before its release to FDA, and then by FDA scientists after it was received. Despite a number of problems, many of which are discussed in the NCI report, concurrence was reached relative to the carcinogenic effect of chloroform in animals. The action proposed by FDA was based not only in consideration of the NCI report but also on other information available, including the CTFA submissions to the FDA Bureau of Foods and the summary of updated experiments presented to the OTC Oral Cavity Products Review Panel of FDA. The necessity for referring this problem to the Toxicology Advisory Committee was discussed at an FDA Bureau of Drugs conference with CTFA representatives prior to publication of the proposal. Based on the data reviewed, discussion with the FDA Bureau of Foods, and discussions with CTFA regarding their data, the Commissioner concludes that it is not necessary to seek the advice of the Toxicology Advisory Committee.

2. One comment expresses the opinion that there is not enough documented evidence to show that products containing chloroform are indeed hazardous to health.

The Commissioner considers the fact that a substance has been shown to be an animal carcinogen must be taken as evidence that it has a potential for carcinogenesis in humans unless there is strong evidence to the contrary. No strong evidence to the contrary has been shown regarding chloroform. Further, the risk to humans through frequent and long term exposure to such a substance in human drug and cosmetic products is contrary to the public health unless the benefit of such exposure clearly outweighs the risk. Any benefits attributed to the use of chloroform in human drug and cosmetic products do not outweigh the attendant risks, particularly in view of the availability of safe and suitable alternate ingredients. The Commissioner concludes that continued use of choloroform in human drug and cosmetic products may cause such products to be injurious to health and is therefore unwarranted. The Commissioner further considers the potential risk posed by chloroform to be a problem necessitating the action taken.

3. One comment expresses the opinion that chloroform does present an imminent health hazard and urged that all drug products containing chloroform be immediately banned and removed from all stores. The comment further requests an immediate public warning urging people to avoid the use of products containing chloroform that are in their possession.

As stated in the preamble of the proposal, because there are no data to show that chloroform is a human carcinogen, and in view of the small amount of chloroform to which an individual might be exposed in using currently marketed chloroform-containing human drug and cosmetic products, the Commissioner has determined that the present risk to the public is minimal and that chloroform-containing products cannot reasonably be considered to constitute an imminent health hazard. Therefore, he does not believe it necessary for consumer protection to order a recall of all currently marketed products containing chloroform or to issue a public warning against the use of such products.

4. One comment requests an exemption from the requirements of the regulation for in vitro diagnostic products containing chloroform. The comment expresses the opinion that such exemption is necessary until legislation is passed which clearly places such products in a category other than human drugs.

The Commissioner advises that the Medical Device Amendments of 1976 (Pub. L. 94-295) became law on May 28, 1976. The new definition of "device" places all in vitro diagnostic products in the device category; therefore, this regulation is not applicable to any such products. No change in the regulation is necessary.

5. Objection was raised that the proposed action invaded a citizen's right of free choice to determine whether to use a product knowing that it may be hazardous. The comment suggests that the label should indicate the facts, good or bad, about a product, but the consumer should then be given the freedom to decide whether to use the product.

The Commissioner disagrees with this comment. Although chloroform-containing human drug and cosmetic products have been on the market for many decades and may have been generally recognized as safe, recent evidence showing chloroform to be an animal carcinogen and its potential for carcinogenesis in humans no longer permit this conclusion. Where scientific evidence indicates that a particular product is no longer safe, the Federal Food, Drug, and Cosmetic Act prohibits its further marketing unless its safety can be demonstrated.

6. Several comments request that the final regulation both permit the continued use of chloroform in the manufacturing process of a human drug or cosmetic product and allow for unavoidable trace residues in the finished product. Some of the comments state that chloroform may occur as an unintended byproduct of the chemical reaction by which the active ingredient in a prescription drug product is synthesized and that total removal of such trace quantities would be technically unfeasible, if not impossible.

The Commissioner advises that the regulation is applicable only to human drug and cosmetic products containing chloroform as an active or inactive ingredient. He further advises that the regulation is not applicable to situations where chloroform is present in residual amounts due to its use as a processing solvent during manufacture of a drug or cosmetic product or to the presence of residual amounts of chloroform as a byproduct resulting from the synthesis of an ingredient in a drug or cosmetic product. The regulation has been revised to clarify this point. The problem raised by the comments is an industrywide problem that is of concern to several government agencies. The FDA is studying the problem intensively to determine the level and extent of chloroform in finished drug and cosmetic products as a result of the manufacturing process and is seeking a resolution of the issue. The Commissioner's decision will be the subject of a separate FEDERAL REGISTER notice if additional steps are necessary to protect the public health.

7. Comments request a change in the proposed effective date of July 8, 1976, to allow firms to dispose of inventories of products which were manufactured or in the process of being manufactured at the time of publication of the proposal on April 9, 1976. One comment states that, if July 8 is the cutoff date for distribution as proposed, manufacturers will be forced to discard existing stocks of these products and will be deluged with stocks returned from the wholesale and retail trade levels. Further, such action could result (1) in the Commissioner's Inflation Impact Analysis being invalid since these costs, which would ultimately be passed to consumers, were

not given adequate consideration and (2) shortage of cough-cold preparations could develop during the coming cold season.

The Commissioner has given extensive consideration to this issue and realizes that the regulation, when effective, will result in destruction of stocks of human drug and cosmetic products on hand at the manufacturer, repacker, relabeler, or own-label distributor levels or those that may be returned from a wholesaler or retailer. He points out, however, that, in the proposal, industry was encouraged to replace chloroform-containing products with reformulated products as soon as possible and in advance of the publication of the final regulation. The potential risk posed by chloroform does not justify continued shipment or use of chloroform-containing human drug and cosmetic products. Therefore, after the effective date of these regulations, any human drug product containing chloroform that is introduced or delivered for introduction into interstate commerce is a new drug and misbranded, and is subject to regulatory action under sections 301, 502, and 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331, 352, and 355). Likewise, after this effective date, any cosmetic product containing chloroform as an ingredient that is introduced or delivered for introduction into interstate commerce is adulterated under section 601(a) of the act (21 U.S.C. 361(a)) and subject to regulatory action. The effective date of these regulations has been extended to July 29, 1976 in that time needed for review of the comments exceeded that originally anticipated. The Commissioner believes that this date should be adhered to in view of all the considerations extensively discussed in the preamble to the proposal. He also believes that this will allow for an orderly replacement of chloroform-containing drug and cosmetic products at the retail level and that there will be an ample supply of such products on the market until reformulated products reach the distribution channels.

The Commissioner advises that in the FEDERAL REGISTER of June 10, 1976 (41 FR 23449), the availability of the NCI report and additional background information was announced by the National Institutes of Health.

The Commissioner also advises that copies of the following references are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852:

1. Bio/dynamics Inc., "A Subacute Toxicity Study of Chloroform in Mice," April 9, 1976.

2. Hill et al., "Genetic Control of Chloroform Toxicity in Mice," *Science*, 190:159, 1975.

3. Charlesworth, F. A., "Patterns of Chloroform Metabolism," *BIBRA Information Bulletin*, 14:225, 1975.

4. Grasso, P. and R. F. Crampton, "The Value of the Mouse in Carcinogenicity Testing," *BIBRA Information Bulletin*, 1975.

5. Cueto, C., Jr. and W. D'Aguanno, memorandum of telephone conversation June 3, 1976.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 301, 502, 505, 601(a), 701(a), 52 Stat. 1042–1043, 1050–1055, as amended (21 U.S.C. 331, 352, 355, 361(a), 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

1. In Part 310, new § 310.513 is added to read as follows:

§ 310.513 Chloroform, use as an ingredient (active or inactive) in drug products.

(a) Chloroform has been used as an ingredient in drug products, such as cough preparations, liniments, and toothpastes. Although considered safe for many years, recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats.

(b) Any drug product containing chloroform as an ingredient is a new drug within the meaning of section 201 (p) of the act and misbranded and is subject to regulatory action under sections 301, 502, and 505 of the act. Any drug product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

(c) Any holder of an approved new drug application for a drug product containing chloroform as an ingredient shall submit to the Food and Drug Administration on or before July 29, 1976 a supplemental application providing for a revised formulation removing chloroform as an ingredient.

(1) The supplemental application shall contain:

(i) A full list of articles used as components and a full statement of the composition of the drug product.

(ii) The date that the composition of the drug product will be changed.

(iii) Data showing that the change in composition does not interfere with any assay or other control procedures used in manufacturing the drug product, or that the assay and other control procedures are revised to make them adequate.

(iv) Data available to establish the stability of the revised formulation and, if the data are too limited to support a conclusion that the drug will retain its declared potency for a reasonable marketing period, a commitment from the applicant:

(*a*) To test the stability of marketed batches at reasonable intervals;

(*b*) To submit the data as they become available; and

(*c*) To recall from the market any batch found to fall outside the approved specifications for the drug.

(v) Copies of the label and all other labeling to be used for the drug product (a total of 12 copies if in final printed form, 4 copies if in draft form).

(2) If such drug product now contains more than one percent chloroform, the revised formulation containing no chloroform shall not be marketed before the receipt of written notice of approval of the supplemental application by the Food and Drug Administration.

(3) If such drug product now contains one percent or less chloroform, the revised formulation containing no chloroform may be marketed, subject to the conditions of § 314.8(e) of this chapter, after submission of the supplemental application but prior to the receipt of written notice of its approval by the Food and Drug Administration.

(d) Any sponsor of a "Notice of Claimed Investigational Exemption for a New Drug" (IND notice) for a drug product containing chloroform as an ingredient shall amend the IND notice on or before July 29, 1976 to revise the formulation removing chloroform as an ingredient.

(e) The Commissioner will initiate action to withdraw approval of an application or terminate an IND notice in accordance with the applicable provisions of section 505 of the act and Parts 312 and 314 of this chapter upon failure of a holder of an approved new drug application or sponsor of an IND notice to comply with the provisions of paragraph (c) or (d) of this section.

2. In Part 700, new § 700.18 is added to read as follows:

§ 700.18 Use of chloroform as an ingredient in cosmetic products.

(a) Chloroform has been used as an ingredient in cosmetic products. Recent information has become available associating chloroform with carcinogenic effects in animals. Studies conducted by the National Cancer Institute have demonstrated that the oral administration of chloroform to mice and rats induced hepatocellular carcinomas (liver cancer) in mice and renal tumors in male rats. Scientific literature indicates that chloroform is absorbed from the gastrointestinal tract, through the respiratory system, and through the skin. The Commissioner concludes that, on the basis of these findings, chloroform is a deleterious substance which may render injurious to users any cosmetic product that contains chloroform as an ingredient.

(b) Any cosmetic product containing chloroform as an ingredient is adulterated and is subject to regulatory action under sections 301 and 601(a) of the Federal Food, Drug, and Cosmetic Act. Any cosmetic product containing chloroform in residual amounts from its use as a processing solvent during manufacture, or as a byproduct from the synthesis of

an ingredient, is not, for the purpose of this section, considered to contain chloroform as an ingredient.

Effective date: These regulations shall become effective July 29, 1976.

(Secs. 301, 502, 505, 601(a), 701(a), 52 Stat. 1042–1043, 1050–1055, as amended (21 U.S.C. 331, 352, 355, 361(a), 371(a)).)

Dated: June 24, 1976.

SAM D. FINE,
Associate Commissioner for Compliance.

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