

Four comments were received in response to the proposal. All the comments concerned the maximum levels of malic acid in confectioners' products. A summary of the comments and the Commissioner's response follows.

The comments expressed the collective view that the proposed maximum levels for malic acid in hard candy (0.9 percent), powdered candy (0.7 percent), and chewing gum (0.7 percent) were too low relative to current manufacturing practice. Two comments recommended elevation of the maximum level in hard candy to 6.9 percent. Two other comments recommended separation of "powdered candy" and "chewing gum" from the "all other foods" category and requested maximum level of 3.0 percent malic acid for both.

The Commissioner has carefully considered the requested modifications in the maximum levels for malic acid in confectioners' products. The Commissioner recognizes that the 1971 National Academy of Sciences/National Research Council (NAS/NRC) survey upon which the proposed maximum usage levels were based, was not comprehensive and, in fact, probably represented only 60 percent of food ingredient users in the United States. The Commissioner has determined that the maximum usage levels for malic acid recommended in the comments for certain confectioners' products represent current good manufacturing practice for those products. Although the newly reported levels of use for malic acid are higher than the levels reported in the 1971 survey and the levels upon which the Select Committee based its safety evaluation, the Commissioner concludes that there are adequate safety data to support higher levels of use in these limited food categories. The maximum usage levels proposed in the comments are, therefore, included in this regulation. It is emphasized, however, that these higher usage levels are not an authorization for use of malic acid at any level higher than is necessary to achieve the intended effect in a specific food.

In accordance with the Commissioner's conclusion, the following regulation has been amended to reflect current good manufacturing practice. The maximum level of malic acid in hard candy is raised to 6.9 percent. Chewing gum is separated from other food categories and has a maximum malic acid level of 3.0 percent. Powdered candy, which is included in the definition of soft candy in 21 CFR

170.3(n)(38), has a maximum malic acid level of 3.0 percent.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

1. In Part 182, as follows:

§ 182.60 [Amended]

a. In § 182.60 *Synthetic flavoring substances and adjuvants*, by deleting the entry for "1-Malic acid."

§ 182.1069 [Deleted]

b. By deleting § 182.1069 *Malic acid*.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

2. In Part 184, by adding new § 184.1069 to read as follows:

§ 184.1069 Malic acid.

(a) Malic acid ($C_4H_6O_5$, CAS Reg. No. of L-form 97-67-6, CAS Reg. No. of DL-form 617-48-1) is the common name for 1-hydroxy-1, 2-ethanedicarboxylic acid. L (+) malic acid, referred to as L-malic acid, occurs naturally in various foods. Racemic DL-malic acid does not occur naturally. It is made commercially by hydration of fumaric acid or maleic acid.

(b) The ingredients meet the specifications of the Food Chemicals Codex, 2d Ed. (1972), as amended by the Second Supplement (1975)¹ which is incorporated by reference.

(c) The ingredients are used as a flavor enhancer as defined in § 170.3(o)(11) of this chapter, flavoring agent and adjuvant as defined in § 170.3(o)(12) of this chapter, and pH control agent as defined in § 170.3(o)(23) of this chapter.

(d) The ingredients are used in food, except baby food, at levels not to exceed good manufacturing practice in accordance with § 184.1(b)(1). Current good manufacturing practice results in a maximum level, as served, of 3.4 percent for nonalcoholic beverages as defined in § 170.3(n)(3) of this chapter; 3.0 percent for chewing gum as defined in § 170.3(n)(6) of this chapter; 0.8 percent for gelatins, puddings, and fillings as defined in § 170.3(n)(22) of this chapter; 6.9 percent for hard candy as defined in

§ 170.3(n)(25) of this chapter; 2.6 percent for jams and jellies as defined in § 170.3(n)(28) of this chapter; 3.5 percent for processed fruits and fruit juices as defined in § 170.3(n)(35) of this chapter; 3.0 percent for soft candy as defined in § 170.3(n)(38) of this chapter; and 0.7 percent for all other food categories.

(e) Prior sanctions for malic acid different from the uses established in this section do not exist or have been waived.

Effective date. This regulation shall be effective May 7, 1979.

(Secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a)))

Dated: March 19, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

Note.—Incorporation by reference was approved by the Director of the Office of the Federal Register on June 20, 1977 and is on file at the Federal Register Library.

[Docket No. 77N-0178]

[FR Doc. 79-10305 Filed 4-5-79; 8:45 am]

BILLING CODE 4110-03-M

21 CFR Parts 182, 184

Succinic Acid; GRAS Status

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This rule affirms that succinic acid is generally recognized as safe (GRAS) as a direct human food ingredient. The safety of this ingredient has been evaluated under the comprehensive safety review being conducted by the agency.

EFFECTIVE DATE: May 7, 1979.

FOR FURTHER INFORMATION CONTACT: Corbin I. Miles, Bureau of Foods (HFF-335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, DC 20204, 202-472-4750.

SUPPLEMENTARY INFORMATION: In the Federal Register of February 3, 1978 (43 FR 4635), The Food and Drug Administration (FDA) proposed to affirm that succinic acid is GRAS for use as a direct human food ingredient. The proposal was based on safety information developed by the Select Committee on GRAS Substances (the Select Committee) and was published in accord with the announced FDA review of the safety of GRAS and prior-sanctioned food ingredients.

Under § 170.35 (21 CFR 170.35), relating to the affirmation of GRAS food ingredients, copies of the scientific literature review on succinic acid, data

¹ Copies may be obtained from: National Academy of Sciences, 2101 Constitution Ave. NW., Washington, D.C. 20037.

on a mutagenic evaluation, and the report of the Select Committee have been made available for public review in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857. Copies of the documents have also been made available for public purchase from the National Technical Information Service, as announced in the proposal.

In addition to proposing to affirm the GRAS status of succinic acid, the Commissioner of Food and Drugs gave public notice that he was unaware of any prior-sanctioned food ingredient use for this ingredient other than for the proposed conditions of use. Persons asserting additional or extended uses, in accordance with approvals granted by the U.S. Department of Agriculture or FDA prior to September 6, 1958, were given notice to submit proof of such a sanction so that the safety of prior-sanctioned uses could be determined at this time. That notice was also an opportunity to have prior-sanctioned uses of succinic acid approved by issuance of an appropriate regulation under Part 181—Prior-Sanctioned Food Ingredients (21 CFR Part 181), provided the prior-sanctioned use could be affirmed as safe on the basis of data now available to the Commissioner. Notice was also given that failure to submit proof of an applicable prior sanction in response to the proposal would constitute a waiver of the right to assert the sanction at any future time.

No reports of a prior-sanctioned use for succinic acid were submitted in response to the proposal. Therefore, in accordance with that proposal, any right to assert a prior sanction for use of succinic acid under conditions different from those set forth in this regulation has been waived.

No comments were received in response to the Commissioner's proposal and supporting data and information on succinic acid. The Commissioner therefore concludes that no change in the proposal to affirm the GRAS status of succinic acid is warranted. Accordingly, it is being promulgated without change.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1), Parts 182 and 184 are amended as follows:

PART 182—SUBSTANCES GENERALLY RECOGNIZED AS SAFE

§ 182.1091 [Deleted]

1. In Part 182 by deleting § 182.1091 *Succinic acid*.

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

2. In Part 184 by adding new § 184.1091 to read as follows:

§ 184.1091 Succinic acid.

(a) Succinic acid ($C_4H_6O_4$, CAS Reg. No. 110-15-6), also referred to as amber acid and ethylenesuccinic acid, is the chemical 1,4-butanedioic acid. It is commercially prepared by hydrogenation of maleic or fumaric acid. It can also be produced by aqueous alkali or acid hydrolysis of succinonitrile.

(b) The ingredient meets specifications of the Food Chemicals Codex, 2d Ed. (1972), which is incorporated by reference.¹

(c) The ingredient is used as a flavor enhancer as defined in § 170.3(o)(11) of this chapter and pH control agent as defined in § 170.3(o)(23) of this chapter.

(d) The ingredient is used in food at levels not to exceed good manufacturing practice in accordance with § 184.1(b)(1). Current good manufacturing practice results in a maximum level, as served, of 0.084 percent in condiments and relishes as defined in § 170.3(n)(8) of this chapter and 0.0061 percent in meat products as defined in § 170.3(n)(29) of this chapter.

(e) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

Effective date. This regulation is effective May 7, 1979.

(Secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a)))

Dated: March 20, 1979.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

Note.—Incorporation by reference was approved on July 10, 1973 by the Director of the Office of the Federal Register and is on file in the Federal Register Library.

[Docket No. 77N-0259]

[FR Doc. 79-10308 Filed 4-5-79; 8:45 am]

BILLING CODE 41-103-M

¹ Copies may be obtained from: The National Academy of Sciences, 2101 Constitution Ave. NW., Washington, DC 20037.

21 CFR Part 201

Drugs: Information Commonly Known; Revocation of Labeling Exemption

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) amends the drug labeling regulations to revoke provisions that exempt certain prescription drugs from the requirement that the dispensing package contain full disclosure labeling (i.e., a package insert). The agency is taking this action because it has concluded that the exemptions are not warranted and that full disclosure labeling is necessary for the safe and effective use of prescription drugs.

EFFECTIVE DATE: October 3, 1979.

FOR FURTHER INFORMATION CONTACT: Michael C. McGrane, Bureau of Drugs (HFD-30), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5220.

SUPPLEMENTARY INFORMATION: In the Federal Register of May 27, 1977 (42 FR 27263), FDA proposed to revoke the provision in § 201.100(c)(2) (21 CFR 201.100(c)(2)) that permits full disclosure labeling (the package insert) to be omitted from the dispensing package of certain prescription drugs and to revoke § 201.160 (21 CFR 201.160), which lists the drugs to which the exemption has applied. Interested persons were given to July 26, 1977, to submit comments on the proposal.

Eight comments were received on the proposal, six from manufacturers of drug products subject to the regulations and two from trade associations. A summary of the comments and the agency's responses to them follows:

1. Three comments objected to the blanket revocation of the exemption from the package insert requirement for the drugs listed in § 201.160. The comments contended that each of the exempted drugs should be examined individually to determine whether its continued exemption from the package insert requirement poses a potential hazard to the public health or whether a specific benefit can be shown to flow from the future use of a package insert with each of the drugs. One comment argued that the proposed revocation of the exemption is based on the agency's opinion about, and experience with, other drugs, but only the identification of a specific risk from the exemption or a specific benefit that will result from its revocation would justify revoking the exemption. Another comment argued

that each drug listed in § 201.160 should be reviewed individually and then removed from the list only if the review shows that the use information for the drug is not commonly known to physicians. One comment contended that, by proposing to revoke the exemption, FDA fails to recognize the scientific merit and judgment in originally establishing the exemption. Another comment argued that the mechanism for exempting drug products from the package insert requirement should be retained. The comment contended that elimination of the mechanism is unnecessary even if some of the drugs currently exempted should have package inserts.

FDA does not agree with these comments. As discussed in the preamble to the proposal, the agency last exempted a drug from the labeling requirements of § 201.100(c)(1) in the *Federal Register* of June 8, 1962 (27 FR 5428). During the 17 years since a drug has been found to qualify for the exemption from the package insert requirement, FDA's experience has shown that risks from the use of a drug may be uncovered long after the drug is first marketed and, thus, after physicians have become familiar with the indications, hazards, and warnings concerning its use. For example, in the *Federal Register* of May 27, 1977 (42 FR 27226), the agency published a final rule ending the exemption under § 201.160 for the drugs that had been reviewed under the agency's Drug Efficacy Study Implementation (DESI) program. Like other drugs on the list, the DESI drugs had been exempted from the package insert requirement of § 201.100(c)(1) because the agency believed the use information for them was commonly known to physicians. The DESI review showed, however, that these drugs were not effective for many of the labeled indications for which they were commonly used.

Conceivably, the agency could attempt to justify the continued exemption for some drugs from the package insert requirement by conducting a review of all of the drugs listed in § 201.160 to determine whether each is safe and effective for its labeled indications under contemporary scientific standards, and whether prescribers are knowledgeable about the use information for each drug. The use of FDA resources to review these drugs periodically for the sole purpose of reducing a few manufacturers' labeling obligations, however, is not justified. The use of FDA resources for that purpose would compromise other programs with greater public health

significance. Revoking the labeling exemption in §§ 201.100(c)(2) and 201.160 merely applies to these drugs the general labeling regulations with which all other prescription drugs are required to comply.

2. One comment argued that section 502(f) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(f)) specifically provides for an exemption such as this.

FDA advises that section 502(f) of the act provides authority for exempting a drug from the requirement that its labeling bear adequate directions for lay use, and § 201.100 (21 CFR 201.100) of the agency's prescription drug labeling regulations exempts all prescription drugs from that requirement. To qualify for the exemption, prescription drugs are required, among other things, to bear a package insert that contains information for practitioners on the safe and effective use of the drug. Sections 201.100(c)(2) and 201.160 thus provided a further exemption from the package insert requirement for certain drugs. Only this latter exemption from the package insert requirement is eliminated under this final rule. The drugs in question are still subject to the provisions of § 201.100 and, accordingly, are still exempt from the "adequate directions for use" requirement under section 502(f) of the act.

3. Two comments objected to the proposal on the ground that requiring package inserts for the drugs exempted under § 201.160 would increase medical health care costs to individual patients and Federal, State, and county health care programs. One comment stated that the cost of the package insert is approximately \$0.05 per package and that revoking the exemption would cost millions of dollars. Another comment argued that, despite the stated intent of the proposal to ensure that physicians have the information necessary to use a drug safely and effectively, the physician would rarely see the package insert.

FDA believes the benefit of the availability of the package insert to physicians and other health professionals, particularly those who dispense the drugs, outweighs the increased costs. Although it is well recognized that labeling for a prescription drug supplied in the form of a package insert is not generally received by the prescriber of the drug, the package insert is nonetheless the official and accepted source of labeling by health professionals and drug manufacturers.

4. Two comments opposed the revocation of the labeling exemption for

sodium chloride injection and sterile water for injection. The comments stated that in small containers the two drugs are most frequently used as vehicles, solvents, or diluents for the administration of other drugs. The comments contended that these uses are well known to physicians and that it would be unreasonable to require separate package inserts for them, particularly when they are often packaged with an active drug for dilution or reconstitution.

FDA advises that if sodium chloride injection or sterile water for injection is marketed alone for use as a vehicle, solvent, or diluent for other medications, the safe and effective use of the drug requires information on its use for those purposes to accompany the product. As stated in paragraph 1 of this preamble, the use of FDA resources to monitor physicians' knowledge about and use of a few drugs for the sole purpose of reducing a few manufacturers' labeling obligations is not justified. The comments assume incorrectly that the marketing of an active drug for reconstitution packaged with a vehicle or diluent would require separate package inserts. In such cases the agency uniformly requires only a single package insert for the drug product and not separate inserts for its components.

5. An association of medical gas manufacturers asked whether the proposed revocation of § 201.160 would include the revocation of § 201.161 (21 CFR 201.161), which exempts carbon dioxide, cyclopropane, ethylene, helium, and nitrous oxide gases intended for drug use from certain labeling requirements, including the labeling requirement under § 201.100(c)(1). The comment argued that § 201.161 was developed as a result of consultations between FDA and representatives of the medical gas industry and, before its revocation is proposed, the original reasons for its promulgation should be considered.

FDA advises that this final rule does not revoke the labeling exemption for certain medical gases under § 201.161.

6. Several comments objected to the proposed effective date for the final regulation of 180 days after the date of publication in the *Federal Register*. The comments argued that the final regulation should apply only to drugs packaged after the effective date or, if the final regulation applies to drugs in the hands of manufacturers or own-label distributors on the effective date, the effective date would discriminate against manufacturers and own-label distributors who sell directly to retailers rather than through wholesalers.

Another comment favored the application of the final regulation to drug products packaged after the effective date because a public health problem has not been shown to exist as a result of the exemptions from full disclosure labeling.

The agency agrees that the effective date should not distinguish between manufacturers, own-label distributors, and other persons, but does not agree that an effective date 180 days after the date of publication of the final regulation is unreasonable. Because package inserts are not now required for these drugs, printing plates and supplies of printed labeling do not exist. In addition, this final regulation merely requires that the affected drugs comply with the general drug labeling regulations that apply to almost all prescription drugs, a requirement that can be implemented within 180 days. Accordingly, the final regulation is effective for all drugs initially introduced or initially delivered for introduction into interstate commerce on and after October 3, 1979.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701, 52 Stat. 1050-1053 as amended, 1055-1056 as amended (21 U.S.C. 352, 355, 371)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Part 201 is amended as follows:

1. In § 201.100 by revising paragraph (c)(2) to read as follows:

§ 201.100 Prescription drugs for human use.

* * * * *

(c) * * *

(2) If the article is subject to section 505, 506, or 507 of the act, the labeling bearing such information is the labeling authorized by the approved new drug application or required as a condition for the certification or the exemption from certification requirements applicable to preparations of insulin or antibiotic drugs.

* * * * *

§ 201.160 [Revoked]

2. By revoking § 201.160 *Drugs; information commonly known.*

Effective date. This regulation is effective October 3, 1979, for any drugs that are subject to these regulations and are initially introduced or initially delivered for introduction into interstate commerce on or after that date.

(Secs. 502, 505, 701, 52 Stat. 1050-1053 as amended, 1055-1056 as amended (21 U.S.C. 352, 355, 371))

Dated: April 2, 1979.

William F. Randolph,
Acting Associate Commissioner for Regulatory Affairs.

[Docket No. 77N-0104]

[FR Doc. 79-10717 Filed 4-5-79; 8:45 am]

BILLING CODE 4110-03-M

21 CFR Parts 436, 449

Method for Griseofulvin Content

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document amends the antibiotic drug regulations by providing for an improved method for determining the griseofulvin content of antibiotic drug products containing griseofulvin. The new method, gas liquid chromatography, replaces two existing methods—the spectrophotometric assay and the microbiological agar diffusion assay.

EFFECTIVE DATE: May 7, 1979.

FOR FURTHER INFORMATION CONTACT: Joan M. Eckert, Bureau of Drugs (HFD-140), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4290.

SUPPLEMENTARY INFORMATION: In the Federal Register of May 26, 1978 (43 FR 22730), and corrected July 14, 1978 (43 FR 30302) and September 8, 1978 (43 FR 40038), the Commissioner of Food and Drugs proposed that the gas liquid chromatography method be adopted as the method specified in the regulations for content determination of the antibiotic drug griseofulvin.

Interested persons were given until July 25, 1978 to submit written comments. A summary of the comments and the Commissioner's response to them follows.

1. Comments from two manufacturers requested that the spectrophotometric assay, an alternative testing method in the current regulations, be retained.

The Commissioner has considered this request but does not believe there is sufficient reason to provide for a specific alternative testing method. As pointed out in the proposal, the gas liquid chromatography method is more accurate and reliable than either the microbiological agar diffusion assay or the spectrophotometric assay methods in the current regulations. However, the Commissioner advises that, under § 436.2 (21 CFR 436.2), manufacturers may use testing methods other than those designated as official methods, provided the results obtained are as accurate as those produced by the official methods.

2. One comment suggested that the testing method should include specific electronic and manual methods for measuring peak areas.

The Commissioner believes that it would be too restrictive to specify the method or methods to be used for peak area measurements. A specific method for measuring peak areas was not included in the proposed method so that any suitable manual or electronic method could be used for this purpose.

3. One manufacturer stated that under the proposed regulation, the life span of its column (proposed § 436.321(c)(1)) was limited to a few days.

The Commissioner advises that in Food and Drug Administration (FDA) laboratory experience, the useful column life has been much longer than that reported by this one respondent. The Commissioner concludes, based on FDA's actual experience and the results of collaborative studies cited in the preamble to the proposal, that the proposed procedure is satisfactory.

4. One comment requested that proposed § 436.321(c)(3) be amended to allow the use of nitrogen as a carrier gas.

The Commissioner recognizes that nitrogen could be used as a carrier gas under appropriate conditions. However, the typical conditions described in the proposed method (i.e., column, packing, and temperature) are specific for the use of helium. These conditions may not be suitable if nitrogen is used in place of helium. As previously mentioned, manufacturers can, under § 436.2, alter the conditions specified to provide optimum results for whatever testing system is used. There is no objection to the use of nitrogen as an alternate testing procedure as long as satisfactory separations and quantitations are obtained.

5. One comment objected to the use of chloroform as a laboratory reagent.

The Commissioner cannot agree with this objection. The amount of chloroform used as a solvent in this method can be safely handled in a chemical hood that would typically be used in this type of laboratory testing operation. The comment is therefore rejected.

6. One manufacturer requested that a high pressure liquid chromatography method be used in place of the proposed gas liquid chromatography method. The comment stated that the requested method is simpler than, and as precise as, the proposed method.

The Commissioner does not consider the comment pertinent to the proposal. The FDA currently has no experience with the high pressure liquid chromatography method for griseofulvin.