Issued in Kansas City, Missouri, on October 7, 1996.

Marvin R. Nuss,

Acting Manager, Small Airplane Directorate, Aircraft Certification Service.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 96N–0144]

Over-the-Counter Drug Products Containing Colloidal Silver Ingredients or Silver Salts

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to establish that all over-the-counter (OTC) drug products containing colloidal silver ingredients or silver salts for internal or external use are not generally recognized as safe and effective and are misbranded. FDA is issuing this proposal because many products containing colloidal silver ingredients or silver salts are being marketed for numerous serious disease conditions and FDA is not aware of any substantial scientific evidence that supports the use of OTC colloidal silver ingredients or silver salts for these disease conditions.

DATES: Written comments by January 13, 1997; written comments on the agency's economic impact determination by January 13, 1997. FDA is proposing that any final rule that may issue based on this proposal become effective 30 days after its date of publication in the Federal Register.

ADDRESSEES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Bradford W. Williams, Center for Drug Evaluation and Research (HFD–310), Food and Drug Administration, 7520 Standish Pl., Rockville, MD 20855, 301–594–0063.

SUPPLEMENTARY INFORMATION:

I. Background

Colloidal silver is a suspension of silver particles in a colloidal base. Historically, a number of colloidal silver/silver colloidal salts have been marketed in the United States. Some of these colloidal silver products were recognized as official articles in the United States Pharmacopeia (U.S.P.) and the National Formulary (N.F.). Colloidal silver iodide (Ref. 1) contained not less than 18 percent and not more than 22 percent silver, with the product diluted for local use to concentrations from 0.05 to 10 percent. Strong silver protein (Ref. 1) contained not less than 7.5 percent and not more than 8.5 percent silver, with the product diluted for local use to concentrations from 0.5 to 10 percent. The 10th edition of the N.F. had a cautionary note for these products that stated: ''Caution: Solutions of Colloidal Silver Iodide should be freshly prepared and should be dispensed in amber-colored bottles,'' and ''Caution: Strong Silver Protein Solutions should be freshly prepared and should be dispensed in amber-colored bottles.''

Mild silver protein (Ref. 2) contained not less than 19 percent and not more than 23 percent silver, with the product diluted for local use to concentrations from 0.1 to 5 percent. The 12th edition of the N.F. had a cautionary note, which stated: ''Caution: Solutions of Mild Silver Protein should be freshly prepared or contain a suitable stabilizer, and should be dispensed in amber-colored bottles.''

Ammoniacal silver nitrate solution (Ref. 2) contained 28.5 to 30.5 percent silver, was made extemporaneously, and was used locally without dilution. Silver nitrate solution (Ref. 3) was made extemporaneously and was used locally at strengths from 0.1 to 10 percent.

None of these formerly recognized colloidal silver preparations has been official in the U.S.P. or the N.F. since 1975. Moreover, of the silver salts evaluated as part of the agency's OTC drug review thus far, none was found to be generally recognized as safe and effective for its intended use(s). These included silver nitrate as an astringent (58 FR 27636, May 10, 1993) and as a smoking deterrent (58 FR 31236, June 1, 1993) and mild silver protein as an ophthalmic anti-infective (57 FR 60416, December 18, 1992). Silver acetate was also evaluated as a smoking deterrent and found not to be generally recognized as safe and effective (58 FR 31236).

II. Recent Developments

In recent years, colloidal silver preparations of unknown formulation have been appearing in retail outlets. These products are labeled for numerous disease conditions, including human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), cancer, tuberculosis, malaria, lupus, syphilis, scarlet fever, shingles, herpes, pneumonia, typhoid, exanthematic typhus, tetanus, variola, scarlatina, erysipelas, rheumatism, candida, staphylococcus and streptococcus infections, tonsillitis, parasites, fungus, bubonic plague, cholera, chronic fatigue, acne, warts, Meniere's disease (syndrome), whooping cough, enlarged prostate, perineal eczema, hemorrhoids, impetigo, ringworm, recurrent boils, burns, and appendicitis.

Several marketers of these products use a labeling brochure that refers to colloidal silver as a treatment or cure for 650 diseases (Ref. 4). Some colloidal silver products have been promoted using reprints of articles, taken from magazines and newspapers, that make claims of extensive health benefits for colloidal silver, similar to the claims listed above. The articles have also been shipped with colloidal silver products, when the products were ordered through the mail (Ref. 5). The dosage form of these colloidal silver products is usually oral, but product labeling also contains directions for topical and, occasionally, intravenous use.

In October 1994, FDA issued Health Fraud Bulletin #19 (Ref. 6) to address the emerging marketing of colloidal silver products offered for serious disease conditions. In that bulletin, the agency stated that it was ''not aware of any substantial scientific evidence which demonstrates that any OTC colloidal silver solution is useful to prevent or treat any serious disease condition.'' The bulletin explained that FDA has not approved a new drug application (NDA) for a colloidal silver product. In addition, the bulletin stated no data or information has been submitted to FDA to document an exemption from the new drug provisions of the Federal Food, Drug, and Cosmetic Act (the act) under the 1938 or 1962 grandfather provisions. The bulletin referred to 21 CFR 314.200(e)(2), which sets forth the type of evidence necessary to support an exemption under a grandfather provision.

III. The ''Grandfather'' Exemption

Some marketers of various colloidal silver preparations claim their products are exempt from the ''new drug'' provisions of section 201(p) of the act (21 U.S.C. 321(p)) under the ''grandfather'' provisions of the 1938 act and the 1962 amendments to the act. The marketers frequently claim that their products were marketed before 1938, that only insubstantial changes have been made in product formulation and labeling since that time, and that

the products' current labeling contains the same representations for use as those contained in the labeling used before 1938.

To qualify for exemption from the ''new drug'' definition under the 1938 ''grandfather'' clause, the drug product must have been subject to the Food and Drugs Act of 1906, before June 25, 1938, and at such time its labeling must have contained the same representations concerning the conditions of its use (section 201(p)(1) of the act). Under the 1962 ''grandfather'' clause, a drug product that, preceding October 9, 1962, (1) Was commercially used or sold in the United States, (2) was not a ''new drug'' as defined in the 1938 act, and (3) was not covered by an approved NDA under the 1938 act, would not be subject to the added requirement of effectiveness ''when intended solely for use, under conditions prescribed, recommended, or suggested in the labeling with respect to such drug.'' (Pub. L. 87–781, sec. 107(c)(4), 76 Stat. 788, note following 21 U.S.C. 321.)

FDA does not believe that any of the currently marketed products qualify for the exemption, because the currently marketed silver products do not appear to be the same as the silver products marketed in the early 1900's. Unlike the silver preparations that were once compendial articles, these new colloidal silver preparations, based on their labeling and/or product analysis, appear to contain less silver than the products marketed historically. Many of the products FDA has sampled lack an ingredient declaration. Samples of some products analyzed by FDA laboratories contained as little as 0.01 percent silver. Analyses showed potency varied from 15.2 percent to 124 percent of the amount of silver declared on the labels. However, FDA has not analyzed the majority of the products on the market and, thus, is unable to state their actual silver content.

Any person seeking to show that a drug comes within a grandfather exemption must prove every essential fact necessary for invocation of the exemption. (See *United States* v. *An Article of Drug * * * ''Bentex Ulcerine*,'' 469 F.2d 875, 878 (5th Cir. 1972), *cert. denied*, 412 U.S. 938 (1973).) Furthermore, the grandfather clause will be strictly construed against one who invokes it. (See *id.; United States* v. *Allan Drug Corp.*, 357 F.2d 713, 718 (10th Cir.), *cert. denied*, 385 U.S. 899 (1966).) A change in the composition or labeling of the product precludes the applicability of the grandfather exemption. (See *USV Pharmaceutical Corp.* v. *Weinberger*, 412 U.S. 655, 663 (1973).)

IV. Evidence of Safety and Effectiveness

FDA is not aware of any body of data that supports the use of colloidal silver for the various conditions listed in the labeling (Refs. 4 and 5) used with currently marketed products.

The 1939 book, ''Argyria, The Pharmacology of Silver'' (Ref. 7), discussed the history and pharmacophysiologic effects of silver administration. It included a summary chapter on the negative effects of argyria, a permanent ashen-grey discoloration of the skin, conjuctiva, and internal organs, resulting from the silver salts. The book also included an index that listed proprietary silver compounds marketed at that time.

Goodman and Gilman described colloidal silver use in earlier editions of *The Pharmacological Basis of Therapeutics* (Refs. 8 and 9). But in the 1980 edition (Ref. 10), Goodman and Gilman stated:

> Claims that mild silver protein penetrates tissue at the site of application because chloride ion does not precipitate the silver are misleading. The large-carrier protein molecule penetrates poorly. Fortunately, the colloidal silver preparations are now in a deserved oblivion.

Goodman and Gilman (Ref. 10) also stated that the indiscriminate use of colloidal silver solutions, especially in the prophylaxis and treatment of respiratory tract infections, probably does more harm than good. They mentioned that there is no acceptable evidence that the routine use of silver solutions for the prophylaxis of colds is at all efficacious, and cases of argyria have resulted from this practice.

Remington's Pharmaceutical Sciences (Ref. 11) and *The Dispensatory of the United States of America* (Ref. 12) state that long-term use of silver preparations could lead to argyria. Concerns about the side effects of argyria may have contributed to reduced medical usage of colloidal silver products.

The Dispensatory of the United States of America (Ref. 12) also stated that there is no justification for the internal use of colloidal silver either theoretically or practically.

Recently, Fung and Bowen (Ref. 13) reviewed the basic chemistry, pharmacokinetics, pharmacology, clinical toxicology, and case reports of adverse events of OTC silver-containing medicinal products, including colloidal silver proteins. They concluded that silver has no known physiologic function and that the risk of using these products exceeds any unsubstantiated benefit.

Fung and Bowen reported that, after ingestion, up to 10 percent of silver salts may be absorbed. Silver is deposited in many organs. The highest concentrations are found in the skin, liver, spleen, and adrenal glands, with lesser deposits in the muscle and brain. Argyria is the most commonly reported adverse event and results from accumulation of silver deposits in the skin below the epidermis. Argyria is effectively irreversible.

As noted in section I. of this document, a number of silver salts were evaluated as part of FDA's OTC drug review, and none was found to be generally recognized as safe and effective for its intended use(s). Accordingly, FDA concludes at this time that no colloidal silver ingredients or silver salts are generally recognized as safe and effective for OTC use.

V. The Agency's Proposal

FDA is proposing to declare all OTC drug products containing colloidal silver ingredients or silver salts as not generally recognized as safe and effective, misbranded, and new drugs within the meaning of section 201(p) of the act. FDA proposes to amend subpart E of part 310 (21 CFR part 310) by adding new § 310.548 for OTC drug products containing colloidal silver ingredients or silver salts. The agency invites any interested parties to collect and submit any existing data and information that support the safety and effectiveness of colloidal silver ingredients or silver salts for any of the uses not already evaluated under the OTC drug review. Safety data should be in accord with § 330.10(a)(4)(i) (21 CFR 330.10(a)(4)(i)) and effectiveness data in accord with § 330.10(a)(4)(ii). The agency will evaluate these data and determine if any colloidal silver ingredients or silver salts should not be included in new § 310.548.

VI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. *National Formulary*, 10th ed., pp. 517 and 520, Rockville, MD, 1955.

2. *National Formulary*, 12th ed., pp. 354–355, Rockville, MD, 1965.

3. *The Pharmacopeia of the United States*, 16th ed., pp. 643–644, Rockville, MD, 1960.

4. Labeling brochure for ''Colloidal Silver.''

5. Reprints of articles and labeling that accompanied samples of colloidal silver shipped through the mail.

6. Food and Drug Administration, Health Fraud Bulletin #19, ''Colloidal Silver,'' October 7, 1994.

7. Hill, W. B., and D. M. Pillsbury, *Argyria, The Pharmacology of Silver*, The Williams & Wilkins Co., Baltimore, 1939.

8. *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, 4th ed., p. 1050, 1970.
9. *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, 5th ed., pp. 930, 931, 999, and 1000, 1975.
10. *The Pharmacological Basis of Therapeutics*, Goodman and Gilman, 6th ed., pp. 976–977, 1980.
11. *Remington's Pharmaceutical Sciences*, 16th ed., pp. 351, 727, and 1111, 1980.
12. *The Dispensatory of the United States of America*, 25th ed., pp. 1234–1236, 1960.
13. Fung, M. C., and D. L. Bowen, ''Silver Products for Medical Indications: Risk-benefit Assessment,'' *Clinical Toxicology*, March 1996.

VII. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the proposed rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of a rule on small entities. Early finalization of the regulatory status of colloidal silver ingredients and silver salts will benefit consumers by the early removal from the marketplace of products for which safety and effectiveness have not been established. This will result in a direct economic savings and public health protection to consumers. In addition, other approved products may be available to treat the conditions. This particular rulemaking for OTC colloidal silver and silver salts drug products is not expected to pose a significant impact on small business because only a limited number of products, the agency estimates fewer than 30, would be covered by this rulemaking. A number of silver ingredients have already been covered in earlier rulemakings in the OTC drug review, and none were found safe and effective for OTC human use. Under the Regulatory Flexibility Act (5 U.S.C. 605(b)), the Commissioner of Food and Drugs certifies that this proposed rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC drug products containing colloidal silver ingredients or silver salts. Comments regarding the impact of this rulemaking on OTC drug products containing colloidal silver ingredients or silver salts should be accompanied by appropriate documentation. The agency is providing a period of 90 days from the date of publication of this proposed rule for comments on this subject to be developed and submitted. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Request for Comments and Data

Interested persons may, on or before January 13, 1997 submit to the Dockets Management Branch (address above) written comments and data in response to the proposed rule. Written comments on the agency's economic impact determination may be submitted on or before January 13, 1997. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments and data should be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments and data may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 310 be amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. New § 310.548 is added to subpart E to read as follows:

§ 310.548 Drug products containing colloidal silver ingredients or silver salts offered over-the-counter (OTC) for the treatment and/or prevention of disease.

(a) Colloidal silver ingredients and silver salts have been marketed in over-the-counter (OTC) drug products for the treatment and prevention of numerous disease conditions. There are serious and complicating aspects to many of the diseases these silver ingredients purport to treat or prevent. Further, there is a lack of adequate data to establish general recognition of the safety and effectiveness of colloidal silver ingredients or silver salts for OTC use in the treatment or prevention of any disease. These ingredients and salts include, but are not limited to, silver proteins, mild silver protein, strong silver protein, silver chloride, and silver iodide.

(b) Any OTC drug product containing colloidal silver ingredients or silver salts that is labeled, represented, or promoted for the treatment and/or prevention of any disease is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product containing colloidal silver or silver salts labeled, represented, or promoted for any OTC drug use is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After (date 30 days after date of publication of the final rule in the Federal Register), any such OTC drug product containing colloidal silver or silver salts initially introduced or

initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: October 9, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–26371 Filed 10–11–96; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[FI–48–95]

RIN 1545–AU09

Amortizable Bond Premium; Hearing Cancellation

AGENCY: Internal Revenue Service, Treasury.

ACTION: Cancellation of notice of public hearing on proposed regulations.

SUMMARY: This document provides notice of cancellation of a public hearing on proposed regulations relating to the federal income tax treatment of bond premium and bond issuance premium. The public hearing originally scheduled for October 23, 1996, beginning at 10:00 a.m. is cancelled.

FOR FURTHER INFORMATION CONTACT: Christina Vasquez of the Regulations Unit, Assistant Chief Counsel (Corporate), (202) 622–6808 (not a toll-free number).

SUPPLEMENTARY INFORMATION: The subject of the public hearing is proposed regulations under section 171 of the Internal Revenue Code. A notice of proposed rulemaking and notice of public hearing appearing in the Federal Register for Thursday, June 27, 1996 (61 FR 33396), announced that a public hearing on the proposed regulations would be held on Wednesday, October 23, 1996, beginning at 10:00 a.m., in the Commissioner's Conference room, room 3313, 1111 Constitution Avenue NW, Washington, D.C.

The public hearing scheduled for Wednesday, October 23, 1996, is cancelled.

Cynthia E. Grigsby,

Chief, Regulations Unit, Assistant Chief Counsel (Corporate).

[FR Doc. 96–26355 Filed 10–11–96; 8:45 am]

BILLING CODE 4830–01–U

26 CFR Part 1

[FI–59–94]

RIN 1545–AU06

Modifications of Bad Debts and Dealer Assignments of National Principal Contracts; Correction

AGENCY: Internal Revenue Service, Treasury.

ACTION: Correction to the notice of proposed rulemaking by cross-reference to temporary regulations.

SUMMARY: This document contains a correction to the notice of proposed rulemaking by cross-reference to temporary regulations (FI–59–94) which was published in the Federal Register on Tuesday, June 25, 1996 (61 FR 32728). The notice of proposed rulemaking by cross-reference to temporary regulations relates to the allowance of a deduction for a partially worthless debt when the terms of a debt instrument have been modified.

FOR FURTHER INFORMATION CONTACT: Craig R. Wojay, (202) 622–3920 (not a toll-free number).

SUPPLEMENTARY INFORMATION:

Background

The notice of proposed rulemaking by cross-reference to temporary regulations that is subject to this correction is under sections 166 and 1001 of the Internal Revenue Code.

Need for Correction

As published, the notice of proposed rulemaking by cross-reference to temporary regulations (FI–59–94) contains an error which may prove to be misleading and is in need of clarification.

Correction of Publication

Accordingly, the publication of the notice of proposed rulemaking by cross-reference to temporary regulations (FI–59–94) which is the subject of FR Doc. 96–15831 is corrected as follows:

On page 32728, column 2, in the heading, the RIN ''RIN 1545–AT08'' is corrected to read ''RIN 1545–AU06''.

Cynthia E. Grigsby,

Chief, Regulations Unit, Assistant Chief Counsel (Corporate).

[FR Doc. 96–26356 Filed 10–11–96; 8:45 am]

BILLING CODE 4830–01–U

Bureau of Alcohol, Tobacco and Firearms

27 CFR Part 55

(Notice No. 841)

RIN: 1512–AB55

Commerce in Explosives

AGENCY: Bureau of Alcohol, Tobacco and Firearms, Treasury.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Bureau of Alcohol, Tobacco and Firearms (ATF) proposes to amend the explosives regulations to require the explosives industry to notify local law enforcement officials and fire departments of sites where explosives are stored or manufactured, increase license and permit fees, eliminate the manufacturer-limited license, amend the definitions of ''fireworks'', ''fireworks nonprocess building'' and ''highway'', and amend the American Table of Distances to conform with the explosives industry's latest revisions. The intended effect of these changes is to protect public safety, eliminate duplication with respect to licensing requirements, and to update references and definitions to reflect current industry and U.S. Department of Transportation terminology.

DATES: Written comments must be received by January 13, 1997.

ADDRESSES: Send written comments to: Chief, Firearms and Explosives Operations Branch, Bureau of Alcohol, Tobacco and Firearms, 650 Massachusetts Avenue, N.W., Washington, DC 20091–0221. ATTN: Notice No. 841.

FOR FURTHER INFORMATION CONTACT: Gail Hosey, Firearms and Explosives Regulatory Division, Bureau of Alcohol, Tobacco and Firearms, 650 Massachusetts Avenue, NW, Washington, DC 20226, (202–927–8310).

SUPPLEMENTARY INFORMATION: The Bureau of Alcohol, Tobacco and Firearms (ATF) and the explosives industry have become increasingly concerned about the number and severity of accidental explosions that have occurred at sites where explosives are stored without the knowledge of State and local officials. Serious explosions have occurred that resulted in multiple deaths and injuries.

In 1988, 6 firefighters were killed as a result of fighting a fire at a construction site where explosives were stored and had not been reported. ATF is concerned with the safety of emergency response personnel responding to fires on sites where