Title 21—Food and Drugs

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

[Docket No. 75N–0003]

SUBCHAPTER D—DRUGS FOR HUMAN USE

PART 310—NEW DRUGS

SUBCHAPTER G—COSMETICS

PART 700—GENERAL

Aerosol Drug and Cosmetic Products Containing Zirconium

AGENCY: Food and Drug Administration, HEW.

ACTION: Final rule.

SUMMARY: The agency is issuing final regulations declaring that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. The Commissioner of Food and Drugs has adopted this position after reviewing an advisory panel report on the use of aerosol antiperspirant products containing zirconium. This regulation will keep these products off the market until safety testing adequate for approval of a new drug application has been done.

EFFECTIVE DATE: September 15, 1977.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of June 5, 1975 (40 FR 24328), the Commissioner proposed that any aerosol drug or cosmetic product containing zirconium is a new drug or an adulterated cosmetic. Interested persons were given until September 3, 1975, to file written comments regarding this proposal. The Commissioner granted a request by The Procter & Gamble Company for an extension of the comment period to October 3, 1975, by notice published in the FEDERAL REGISTER of August 21, 1975 (40 FR 36574), to permit time for compilation of extensive new data that arguably would resolve the issues of toxicity raised in the proposal. Data and comments filed with the office of the Hearing Clerk, Food and Drug Administration, up to March 26, 1976, have been considered in order to include as much of the complex data as possible in reviewing the issue.

The June 5, 1975 proposal was in response to a report submitted to the Commissioner by the over-the-counter (OTC) Panel on Review of Antiperspirant Drug Products. This panel concluded in their report that zirconium compounds have caused skin granulomas and toxic effects in the lungs and other organs of experimental animals and expressed concern about the potential toxicity of such compounds when used in humans over an extended period of time. Although extensive animal toxicity data were received, these data failed to provide a basis for establishment of a safe level for long-term use. The panel also concluded that the benefit likely to be derived from the use of zirconium-containing aerosol antiperspirants is unsupportable in view of the risks involved. The benefit from the use of zirconium-containing aerosol antiperspirants is available to consumers from other products that are generally recognized as safe.

Therefore, the panel recommended that:

1. All zirconium-containing aerosol antiperspirants be placed in Category II (not generally recognized as safe), and

2. Because conclusive testing to establish the safety might take years to accomplish, the Commissioner should take immediate steps to remove these ingredients from interstate commerce until safety has been demonstrated.

The Commissioner, after an extensive review of the data and conclusions of the panel, adopted their position in the June 5, 1975 proposal. He further concluded that, based on this adverse benefit-to-risk ratio and the recommendation for prompt action, any delay in action regarding the use of these drug and cosmetic products was unjustified and contrary to the public interest. He decided that this action should not await the final report of the OTC Panel on Review of Antiperspirant Drug Products but should be implemented as soon as possible. In fact, companies who submitted data to the panel on zirconium-containing aerosol antiperspirants have already indicated compliance with the panel's recommendation (see below).

The Commissioner reviewed extensively all of the comments to the proposal and all new data submitted through March 26, 1976. Because of the complexity of the data, he further solicited comments from experts in inhalation toxicity specifically for the purpose of reviewing the new data submitted in response to the June 5, 1975 proposal.

The Commissioner is aware that in May 1976 the United States manufacturers of zirconium-containing aerosol antiperspirants announced voluntary cessation of the manufacture of the zirconium complexes discussed in the June 5, 1975 proposal. He also has information that no further manufacturing of OTC products containing this ingredient as an antiperspirant in aerosol form has occurred since that time, although distribution of some previously manufactured products had continued into October 1976.

The agency received 21 comments from consumers supporting the proposed action and 10 from 3 pharmaceutical manufacturers against the proposed action. A summary of the significant comments to the proposal and the Commissioner's conclusions are as follows:

1. *Inhalation toxicity.* One comment stated that zirconium aluminum glycine complex (ZAG) and aluminum chlorhydrate elicited only the effects of a nonspecific irritant. New studies, not available to the Commissioner when he issued his proposal, were submitted by several manufacturers to illustrate this nonspecific irritant effect. They consisted of several short-term, high concentration exposure tests.

The Commissioner recognizes that short-term, acute aerosol animal studies are helpful in establishing a complete toxicity profile. However, he is obliged to assess the toxicity of zirconium compounds in their intended use, i.e., daily application over a period of years, perhaps decades. Acute and subchronic (less than 90 days) toxicity studies, while helpful, cannot be relied upon to extrapolate long-term effects. Granulomatous lung disease is chronic in nature and develops slowly. Long-term studies are particularly important when consideration is given to a large population that may be at special risk by virtue of preexisting impairment of lung function, e.g., asthmatics, individuals with emphysema, or even heavy cigarette smokers. Consequently, the Commissioner concludes that the acute and subchronic studies submitted do not address the considerations needed to resolve the safety problems posed by long-term use.

Some of the studies submitted were 6-month and 1-year interim reports on chronic inhalation studies in monkeys and rats. The submitters stated that the limited results available to date suggest that exposure of monkeys and rats over a 1-year period did not produce obvious pulmonary changes.

While the Commissioner believes that this information is encouraging, the study has not been completed. The Commissioner is unable to make a decision based on such incomplete data. Consequently, the issue of long-term toxicity remains unresolved.

2. *Granuloma formation.* One comment stated that ZAG produced only the effects of foreign body irritants and only after extreme overdosing. A study was submitted in which hamsters were intratracheally infused with ZAG, sodium zirconium lactate, and aluminum chlorhydrate. Lesions were produced in all animals. There were qualitative differences in the lesions produced by ZAG and aluminum chlorhydrate. ZAG tended to produce a lesion with granulomatous inflammation predominating, whereas aluminum chlorhydrate produced, primarily, bronchiolar adenomatoid lesions (a nonspecific microscopic lesion of the terminal bronchioles).

In another study submitted by the same commentor, single intradermal injections of ZAG and sodium zirconium lactate were given to each of nine guinea pigs. All animals were subsequently challenged by intradermal injections of the same compounds. Beryllium sulfate was included as a positive control and elicited the classical exudative skin reaction indicative of delayed hypersensitivity. ZAG was found to produce granulomas in the skin of all animals receiving as little as 1 microgram of zirconium. The lesions were described as a varying combination of necrosis of dermal collagen and giant and epithelial [sic] cells. The Commissioner believes that the presence of epithelioid cells is indicative of a high-turnover granuloma

and not the simple deposition of an inert foreign body.

In a third study from the same commentor, sodium zirconium lactate, ZAG, and aluminum chlorhydrate were tested. In this study, ZAG was also shown to cause granulomatous lesions.

The Commissioner concludes that exposure to ZAG and other zirconium salts by the inhalation route still tends to be associated with granuloma formation. Assertions of safety and submissions designed to demonstrate that safety leave this issue unresolved.

3. *Safety versus toxicity testing.* One commentor submitted partially complete long-term inhalation studies to demonstrate safety.

Because toxic effects have been found in animals exposed to one zirconium-containing aerosol antiperspirant, the Commissioner concure with the panel's report that modern toxicological research dictates that the dose-response curve of the material be determined so that safety factors can be estimated under normal usage and potential abuse conditions. The partially complete long-term inhalation studies performed and submitted with the comment contain as insufficient range of dosages to reasonably determine the dose-response relationship. Even with the completion of the long-term inhalation studies, the Food and Drug Administration (FDA) will still lack sufficient data needed to establish such a curve. The Commissioner therefore concludes that the acute, short-term, and chronic toxicity studies submitted by the commentor fail to resolve the long-term toxicity issues raised in the June 5, 1975 proposal, and, even if present chronic inhalation studies were complete, they would still be insufficient to resolve these issues.

4. *Skin irritation and sensitization.* Several comments alleged that no sensitization occurs with ZAG, and studies were submitted to support this contention.

The panel stated that no adequate tests had been submitted to show lack of potential for zirconium to cause irritancy and sensitization. Subsequent to the proposal, studies were presented to assess the potential of zirconium compounds to cause sensitization. In these studies, animals (monkeys, guinea pigs, hamsters, and rabbits) were intradermally administered either a zirconium compound or a control substance (a substance known to produce sensitization: in these experiments, either ovalbumin or beryllium sulfate). From these studies, no evidence was found that ZAG produced sensitization.

The Commissioner reviewed the animal studies designed to produce allergic response or sensitization. Under conditions of the tests, there was no evidence that ZAG produced sensitization. The Commissioner agrees that these animal studies have shown that ZAG does not produce a sensitization reaction under these test conditions and is therefore not considered acutely allergenic. However, he is unable to conclude, on the basis of the data submitted with the comments, that ZAG or other zirconium compounds would not yield sensitizing derivatives if retained for long periods of time in lung tissue. It is not predictable from these tests if there would be sensitization as a result of long-term exposure in humans.

5. *Particle size effets.* Two manufacturers stated that their products have been reformulated such that all zirconium- containing aerosol particles are 10 microns or larger in diameter. According to the Task Group on Lung Dynamics of the International Radiological Protection Commission report (Health Physics 12:173–207, 1966, a copy of which is on file with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857), all inhaled particles larger than 10 microns are deposited in the tracheobronchial and nasopharnygeal regions and will not reach the deep portions of the lung. Particles lodging in the upper respiratory tract would be cleared from the body via natural mucociliary escalator (normal lung clearance mechanism).

The Commissioner agrees that if the production of such a formulation is technically feasible, the possibility of deep lung deposition and the attendant local pulmonary responses discussed in the June 5, 1975 proposal would be substantially reduced. However, the production of aerosols with most of the particles greater than 10 microns does not eliminate all particles that may reach the pulmonary region (respiratory bronchioles and alveoli). Particle size distribution should be determined by impaction (a method for measuring particles) of the macrospherical (larger size) particles with optical or electron microscopy confirmation of the particle size characteristics. Such data have yet to be submitted to FDA.

The change in particle size will change the deposition sites from the deep lung to the upper respiratory tract and nasopharyngeal areas. The Commissioner feels that the anatomical redistribution of deposition sites does not necessarily alter zirconium toxicity, only the possible site of the lesion. Granulomas of the upper respiratory tract and gastrointestinal tract have been reported with other substances.

The Commissioner concludes that further particle sizing data are required and that the potential for zirconium compounds to cause graulomas in the upper respiratory tract or the nasopharyngeal area must also be investigated. In addition, because zirconium-containing aerosol antiperspirants produce relatively insoluble particles, the amount may increase from daily dosing such that the ability of normal lung clearance mechanisms (mucociliary, lymphatic, and circulatory removal) to cope with these particles may be inhibited. Investigation, particularly with respect to the length of time particles remain in the lung, the time required for clearing such particles from the lung, and the specific mechanism of clearance is mandatory.

6. *Cytotoxicity.* Two commentors reported testing in progress to determine the cytotoxic potential of zirconium complexes. These studies were designed to assess the cytotoxic and functional effects on rabbit and human alveolar macrophages (specialized cells in the lung).

The Commissioner has reviewed the limited interim data to date and is aware that the results do not indicate that ZAG or other complexes are directly toxic to replicating cells in vitro. However, the Commissioner believes that the tests to date are not sufficient to allow him to conclude that the complexes, some degradation product thereof, or a catalyzed reaction may not produce toxic cellular effects. Further, these studies have not been completed and the Commissioner concludes that there are insufficient data on which to base a decision.

7. *Allergenicity/hypersensitivity.* Five studies were submitted with two comments to illustrate lack of potential for allergenicity of ZAG. ZAG and other zirconium salts were administered by intratracheal infusion or by means of a skin patch to induce sensitization. The animals were subsequently tested for sensitization with the same material. Although lesions were produced, no sensitization was said to occur.

In all these studies, either the frequency of inoculation was inadequate or the duration was too short. The panel indicated that "single-shot" attempts to induce hypersensitivity were often ineffective. Potent sensitizers like beryllium sulfate have required as long as 16 months to produce sensitivity.

In all these tests, the inoculum was administered either intratracheally or via the skin patch. Inhaled particles possess different characteristics than particles intratracheally infused, insufflated, or injected. They are distributed in a manner completely different from those introduced by other methods. The panel emphasized this point in the proposal. In normal usage, the product would be applied and inhaled daily over a period of years. Inhalation of particles over this period of time could theoretically produce sensitization. Mucosal surfaces provide a uniquely active site for the development of immunologic hypersensitivity. None of the allergenicity/hypersensitivity tests received thus far approximate actual use conditions which allow the Commissioner to make a safety determination.

8. *Chemical identity.* One comment discussed the means of production of the macrospherical material that has an increased average particle size. The comment concluded that the data submitted during the comment period show that ZAG in the macrospherical formulation is chemically identical to the smaller particle size material. Furthermore, a recently developed method for utilizing differential scanning colorimetry to additionally characterize ZAG was reported, thus defining the chemical identity and integrity of ZAG and differentiating it from other zirconium aluminum compounds. However, in contrast,

another comment was received reflecting the opinion of a noted expert on the chemical reactions of zirconium and zirconium complexes. This comment pointed out that the zirconium materials presently used in antiperspirants are complex polymeric compounds. Though chemical analysis has enabled their empirical formulae to be determined, the molecular structures of these materials are still unknown. The polymerization process produces not a single molecular entity, but a range of structures varying in molecular weights. Depending on the solvent system, acidity of the solution, and the time of exposure to that acidity, a variety of polymeric species will form. The polymers can differ not only in molecular weight but can differ topologically (spatial relationship of atoms within the molecule).

The Commissioner agrees that the chemical tests submitted show similarity in chemical identity between the small particle and macrospherical formulation. However, data submitted in the comments show that the identification of ZAG powder by a single analytical technique has not yet been achieved. In addition, in attempting to characterize the regular and macrospherical forms, it was found that both forms of the aerosol antiperspirant material are slightly soluble in human serum albumin. Polymeric zirconium compounds are known to be excellent catalysts for a host of chemical reactions. The Commissioner is concerned that a possible explanation of the different toxic effects reported for zirconium-containing aerosol antiperspirant ingredients may be found in the variety of polymeric species which may form depending on the conditions of chemical reaction.

The Commissioner recognizes that many aspects of zirconium chemistry have not been completely determined and concludes that sufficient data have not been submitted concerning the formation of different polymeric species, the activity of zirconium complexes as catalysts, and the potential interactions of zirconium complexes with cellular constituents.

Regulatory Action

Because it appears that conclusive testing to establish the safety of zirconium-containing aerosol antiperspirants would take years to accomplish, and because during that time millions of consumers would be unnecessarily subjected to risk, the Commissioner has decided to stop movement of these agents in interstate commerce until safety testing adequate for approval of a new drug application has been done, as recommended in the proposed rule making.

Based on the estimates of outstanding stocks of zirconium-containing aerosol antiperspirants currently on the market, and in keeping with the conclusions presented in the proposed rule making that the major safety issue is attributable to prolonged use, the Commissioner does not at this time anticipate that a recall of previously marketed zirconium-containing aerosol drug and cosmetic products is necessary to protect the public health. Upon the effective date of this final order, FDA will conduct an appropriate surveillance program to assure that no substantial stocks of zirconium-containing aerosol drug and cosmetic products remain on the market.

The available toxicological data indicate that zirconium compounds may be responsible for human skin granulomas as well as toxic effects in the lungs and other internal organs of test animals. Accordingly, these ingredients in aerosol formulations are not generally recognized as safe, and the Commissioner considers any drug product containing zirconium in aerosol form to be a new drug. Furthermore, the Commissioner believes that the available information is sufficient to show that aerosol cosmetic products containing zirconium may be injurious to users. The regulation as proposed stated that regulatory action was being taken with respect to cosmetic products "[b]ased upon the lack of toxicological data adequate to establish a safe level for use * * *." The final regulation relating to cosmetic products has been revised to delete this phrase, to identify the risks from zirconium use that are of concern, and to refer to the statutory test for determining when a product is adulterated. This change brings the regulation into conformity with the format used in Part 700, Subpart B, for requirements for specific cosmetic products, which inadvertently was not followed in the proposed regulation. As revised, the regulations states the considerations on which the Commissioner relied in issuing the proposed and final regulations finding that aerosol cosmetic products containing zirconium are adulterated.

This determination does not affect zirconium-containing, nonaerosol antiperspirspants that are being reviewed by the OTC Antiperspirant Panel. Determination of their safety and effectiveness will progress through the normal administrative process of the OTC review (21 CFR 330.10).

The Commissioner has carefully considered the environmental effects of the regulation and, because the action will not significantly affect the quality of the human environment, has concluded that an environmental impact statement is not required. A copy of the environmental impact analysis report and environmental impact assessment are on file with the Hearing Clerk, Food and Drug Administration.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 505, 601(a), 701(a), 52 Stat. 1052–1055, as amended (21 U.S.C. 355, 361(a), 371(a))) and under authority delegated to him (21 CFR 5.1), the Commissioner is amending Parts 310 and 700 as follows:

1. In Part 310, by adding new § 310.510 to Subpart E to read as follows:

§ 310.510 Use of aerosol drug products containing zirconium.

(a) Aerosol products containing zirconium have been used in over-the-counter drug products as antiperspirants. Based upon the lack of toxicological data adequate to establish a safe level for use and the adverse benefit-to-risk ratio, such aerosol products containing zirconium cannot be considered generally recognized as safe for use in drug products. The benefit from using aerosol drug products containing zirconium is insignificant when compared to the risk. Safer alternative antiperspirant products are available.

(b) Any aerosol drug product containing zirconium is a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which an approved new drug application pursuant to section 505 of the act and Part 314 of this chapter is required for marketing.

(c) A completed and signed "Notice of Claimed Investigational Exemption for a New Drug" (Form FD–1571), as set forth in § 312.1 of this chapter, is required to cover clinical investigations designed to obtain evidence that such preparation is safe for the purpose intended.

(d) Any such drug product introduced in interstate commerce after September 15, 1977 that is not in compliance with this section is subject to regulatory action.

2. In Part 700, by adding new § 700.16 to Subpart B to read as follows:

§ 700.16 Use of aerosol cosmetic products containing zirconium.

(a) Zirconium-containing complexes have been used as an ingredient in cosmetics and/or cosmetics that are also drugs, as, for example, aerosol antiperspirants. Evidence indicates that certain zirconium compounds have caused human skin granulomas and toxic effects in the lungs and other organs of experimental animals. When used in aerosol form, some zirconium will reach the deep portions of the lungs of users. The lung is an organ, like skin, subject to the development of granulomas. Unlike the skin, the lung will not reveal the presence of granulomatous changes until they have become advanced and, in some cases, permanent. It is the view of the Commissioner that zirconium is a deleterious substance that may render any cosmetic aerosol product that contains it injurious to users.

(b) Any aerosol cosmetic product containing zirconium is deemed to be adulterated under section 601(a) of the Federal Food, Drug, and Cosmetic Act.

(c) Any such cosmetic product introduced in interstate commerce after September 15, 1977 is subject to regulatory action.

Effective date: This order shall be effective on September 15, 1977.

(Secs. 505, 601(a), 701(a), 52 Stat. 1052–1055, as amended (21 U.S.C. 355, 361(a), 371(a)).)

Dated: August 6, 1977.

Donald Kennedy,
Commissioner of Food and Drugs.

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