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# REPORT BY THE Comptroller General

113187  
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OF THE UNITED STATES

## FDA's Regulation Of Gentian Violet Appears Reasonable

The Food and Drug Administration has not approved the use of gentian violet as a food additive or as an animal drug. GAO found no indication that FDA's position was unreasonable or that regulatory actions taken by FDA were improper. In 9 of 10 cases where FDA regulatory actions were challenged in court, the courts agreed with FDA's position on the use of gentian violet for veterinary purposes.

GAO also reviewed allegations of FDA harassment of three firms that have sold or requested FDA approval to sell veterinary products containing gentian violet. No evidence was found to substantiate these charges.



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COMPTROLLER GENERAL OF THE UNITED STATES  
WASHINGTON, D.C. 20548

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✓ The Honorable Herman E. Talmadge, Chairman  
Committee on Agriculture, Nutrition, and  
Forestry  
United States Senate

SEN 06100

The Honorable Jesse Helms<sup>A.</sup>  
Ranking Minority Member  
Committee on Agriculture, Nutrition,  
and Forestry  
United States Senate

This report discusses the Food and Drug Administration's (FDA's) regulation of gentian violet as an additive to animal feeds and as an animal drug.

The report addresses concerns about whether FDA acted improperly in regulating gentian violet and discusses FDA's dealings with three companies that have marketed this product--Animal Health Products, Inc., Dan-Mar Enterprises, Inc., and Narengo, Inc. We found no evidence that (1) FDA officials exhibited malice against those companies, (2) FDA's regulatory machinery had been improperly used to force any of the companies off the market, or (3) FDA had been unresponsive to efforts made by the companies to resolve problems concerning the adequacy of safety and effectiveness data they submitted to FDA.

As arranged with the Senate Committee on Agriculture, Nutrition, and Forestry, 3 days after the date of this report a copy will be sent to Senator John Danforth. Unless you or Senator Danforth publicly announce its contents earlier, we plan no further distribution of the report until 30 days from the date of the report. At that time, we will send copies to the Department of Health and Human Services, the three companies involved, other interested parties, and others upon request.

*Allen A. Stairs*

Comptroller General  
of the United States

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D I G E S T

Gentian violet, a dye, has been used as an animal drug to treat many diseases and as an additive in animal feed to inhibit mold. If drugs or food are to be used in food-producing animals, the Food and Drug Administration (FDA) must approve the safety of any residues in food. FDA has not approved gentian violet for these uses and its actions in regulating gentian violet have been questioned.

GAO was asked to determine whether

- some FDA officials exhibited malice against certain companies and individuals,
- FDA's regulatory machinery was improperly used to force some companies out of the market, and
- FDA was unresponsive to efforts made in good faith by three companies to resolve problems concerning the adequacy of safety and effectiveness data they submitted to FDA. These three companies have sold or requested FDA approval to sell veterinary products containing gentian violet.

GAO found no evidence to substantiate any of these charges.

FDA has determined that, when used for veterinary purposes, gentian violet is either a food additive or a new animal drug as defined by the Food, Drug, and Cosmetic Act, as amended. As such, gentian violet may not be marketed until sponsors have obtained FDA approval.

Tear Sheet. Upon removal, the report cover date should be noted hereon.

GENTIAN VIOLET NOT APPROVED  
AS VETERINARY MEDICINE

As of June 1980, FDA had not approved gentian violet for use in veterinary products. Two firms in GAO's review, believing the history of gentian violet use and other data demonstrated safety and effectiveness, had sold products containing gentian violet.

FDA has also determined that gentian violet does not qualify for interim food additive status. Interim status would allow products containing gentian violet to be sold while tests of safety were conducted. In two separate cases the courts have upheld FDA's determination of the status of gentian violet as an unapproved food additive and/or new animal drug.

Gentian violet is currently available as a nonprescription drug for human use. As a product to control fungus and intestinal parasites, it is used for short periods of time; therefore, the pattern of human exposure differs from that of animal drugs. FDA's Bureau of Drugs is currently evaluating whether gentian violet is generally recognized as safe and effective and whether it should continue to be available as an over-the-counter drug. (See ch. 2.)

SAFETY AND EFFECTIVENESS  
NOT DEMONSTRATED

The safety and effectiveness of gentian violet in veterinary use have not been demonstrated. The Food, Drug, and Cosmetic Act and FDA regulations require that, before a food additive petition or new animal drug application can be approved, a product must be shown to be safe by the sponsor. Animal drugs must be shown to be effective and food additives to have utility at the proposed level of use. The acting director, Division of Drugs for Avian Species, FDA Bureau of Veterinary Medicine, told GAO that the criteria for demonstrating effectiveness and utility are similar.

According to FDA, the safety of gentian violet must be demonstrated in long-term tests designed to assess whether or not gentian violet is carcinogenic (causes cancer). These tests are necessary because gentian violet is a suspected carcinogen and also because the proposed uses could result in chronic human exposure to its residues.

The effectiveness or utility of gentian violet as a mold inhibitor in animal feeds also has not been demonstrated. No firm has submitted adequate data to satisfy the safety and effectiveness requirements. Although three firms have indicated that they disagree with FDA's determination that long-term tests are needed, none has used the appeal procedures established by the act and FDA regulations. (See ch. 3.)

#### FDA REGULATORY ACTIONS

FDA takes certain regulatory actions to assure that only safe and effective food additives and animal drugs are marketed. These actions include (1) inspections, (2) adverse findings/warning letters, (3) regulatory letters, (4) product seizures, and (5) injunctions and criminal prosecution. GAO's review disclosed that the regulatory actions taken by FDA against the three firms were not unreasonable in view of FDA's decisions that gentian violet products are unapproved as food additives and new animal drugs. FDA's determinations have, in 9 of 10 cases, been upheld by the courts. (See ch. 4 and app. III.)

#### ALLEGATIONS OF HARASSMENT

One of the firms reviewed--Naremco--alleged that certain actions taken by FDA were unreasonable, overstepped agency authority, and/or deliberately attempted to discredit or drive the firm out of business. While

some statements made by FDA officials to Members of Congress were inaccurate, GAO could not conclude that these were deliberate attempts to discredit or drive the firm out of business. Officials of the other two firms reviewed--AHP and Dan-Mar Enterprises--told GAO that they believed their failure to gain approval for their products was a result of FDA's dealings with Naremco. These officials said that they thought FDA's refusal to permit them to market gentian violet products was the result of FDA's desire to restrict Naremco from selling such products. (See ch. 5.)

#### AGENCY AND INDUSTRY COMMENTS

The Department of Health and Human Services said that in general it agreed with the contents and conclusions of this report.

AHP through its attorney, stated that the report contained a fair and accurate representation of the information the firm provided to GAO.

The other two firms in our review--Dan-Mar Enterprises and Naremco--declined to comment. (See ch. 6.)



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ABBREVIATIONS

AHP	Animal Health Products
BVM	Bureau of Veterinary Medicine
FAP	food additive petition
FDA	Food and Drug Administration
FD&C	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
NADA	new animal drug application
NCTR	National Center for Toxicological Research
USDA	U.S. Department of Agriculture



## CHAPTER 1

### INTRODUCTION

In a January 4, 1979, letter, Senator Herman Talmadge, Chairman, Committee on Agriculture, Nutrition, and Forestry, and Senator Robert Dole requested that we study the Food and Drug Administration's (FDA's) activities regarding gentian violet. In particular, we were to review FDA's dealings with Naremco, Dan-Mar Enterprises and Animal Health Products (AHP). These firms have marketed and/or attempted to obtain FDA approval to market veterinary products containing gentian violet. The requestors were concerned with the economic stress that FDA decisions placed on manufacturers of gentian violet and that livestock and poultry producers might be deprived of a needed product.

The Senators requested that we prepare a case study of FDA's dealings with the three companies, including the basis for any decisions rendered by FDA, whether FDA's actions conformed to established policies and procedures, and whether

- some FDA officials exhibited malice against certain companies and individuals,
- FDA's regulatory machinery was improperly used to force certain companies out of the market, and
- FDA was unresponsive to efforts made in good faith by companies to resolve problems with their applications.

### WHAT IS GENTIAN VIOLET AND HOW IS IT USED?

Gentian violet is a dye with a molecular structure belonging to a chemical class generally known as di- and tri-aminophenylmethanes. Gentian violet has been used to control fungus and intestinal parasites in humans, as an antiinfectant for children, as an additive for livestock feed to inhibit mold, and as an animal drug to treat many diseases.

Gentian violet has been available for use as an animal feed additive and an animal drug since the mid-1950s. Initially, it was included in products sold for the prevention and/or treatment of nonspecific intestinal diseases of swine and poultry and as a vitamin/mineral supplement for cattle. During the mid-1970s, gentian violet was sold as a

single-active-ingredient product to reduce spoilage in feed caused by fungus and mold organisms and to help control and treat crop mycosis <sup>1/</sup> in chickens and turkeys. Gentian violet, when sold for use as an additive in animal feed, is regulated as a food additive. When sold for use as a therapeutic agent in animals, it is regulated as a new animal drug.

REGULATION OF NEW ANIMAL  
DRUGS AND FOOD ADDITIVES

Basic legal authority for regulating new animal drugs and food additives is contained in the Federal Food, Drug, and Cosmetic (FD&C) Act, as amended (21 U.S.C. 301 et seq.), which is administered by FDA. The act requires that a sponsor (manufacturer or other entity seeking to market a new animal drug or food additive in interstate commerce) file a new animal drug application (NADA) or food additive petition (FAP) with FDA and obtain its approval of safety and effectiveness, before introducing the product into interstate commerce. If a new animal drug or food additive is to be used in food-producing animals, FDA must also approve the safety of any residues in food.

FDA's Bureau of Veterinary Medicine (BVM) <sup>2/</sup> has primary responsibility for regulating veterinary products, including reviewing FAPs and NADAs and conducting surveillance and compliance activities. FDA's Bureau of Foods assists BVM by reviewing data submitted to demonstrate the safety of any drug or food additive-related residues in food.

The 1938 amendments to the Food and Drug Act of 1906 required that all drugs be shown to be safe by scientific procedures under the conditions of their intended use before marketing. The amendments permitted the continued marketing of drugs that had been marketed before 1938.

FDA's regulatory authority over new animal drugs was broadened by two amendments to the FD&C Act--the Food Additive Amendments of 1958 (Public Law 85-929) and the Drug Amendments of 1962 (Public Law 87-781).

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<sup>1/</sup>A disease caused by fungus or mold found in poultry.

<sup>2/</sup>BVM was established on January 1, 1966. Before then, the Bureau of Medicine had responsibility for regulating both human and animal drugs. The Bureaus of Foods and Drugs were established February 1, 1970. Before then, the functions of the Bureaus of Foods and Drugs were divided among the former Bureaus of Medicine, Science, and Compliance.

Before the 1958 amendments, the burden of proof that a drug was safe for the conditions of its intended use was on FDA. The 1958 amendments shifted this burden to the manufacturer by authorizing FDA to issue regulations prescribing the conditions under which an animal drug may be safely used in food-producing animals. The 1962 amendments added the requirement that drugs be proven effective.

The 1958 amendments also contain a specific requirement for preclearing certain food additives for safety by scientific procedures before such substances can be used in foods and before they can be marketed. Food additives marketed before the 1958 amendments could continue to be marketed if they were generally recognized as safe through common use. Any changes to the manufacturing of a product or in the claims made for a product, however, result in the drug or food additive being subject to current requirements of safety and/or effectiveness.

In 1968, the animal drug amendments were enacted. These amendments established a new section of the act dealing specifically with animal drugs. FDA's authority and responsibility for these drugs remained unchanged.

#### SCOPE OF REVIEW

We reviewed legislation, regulations, and practices relating to FDA's regulation of veterinary medicine and especially their application in regulating gentian violet from 1955 to the present. We examined correspondence and other files maintained by FDA for the three companies. We also reviewed records relating to inspections, other regulatory actions taken by FDA, and judicial proceedings. We interviewed officials from FDA's BVM, Bureau of Foods, Bureau of Drugs, General Counsel's office, and the U.S. Department of Agriculture (USDA).

We also interviewed officials from Naremco, Dan-Mar Enterprises, and AHP and reviewed data provided to us by these officials. Dan-Mar is no longer in business.

## CHAPTER 2

### STATUS OF GENTIAN VIOLET

FDA has determined that gentian violet, when used or sold for use in therapeutic purposes in animals, is a new animal drug and, when used or sold for use as an additive to animal feed, is a food additive that may not be marketed without prior FDA approval. FDA has not approved gentian violet for any use in veterinary medicine.

We found that:

- Gentian violet, as a food additive, is not generally recognized as safe and, as a new animal drug, is not generally recognized by FDA as safe and effective.
- Federal court decisions handed down in April 1977 and September 1978 have upheld FDA's determination of the status of gentian violet.
- Gentian violet is not exempt by the grandfather clause 1/ of the FD&C Act.
- Gentian violet does not qualify for interim food additive status.
- Gentian violet is generally recognized as safe and effective by FDA as an over-the-counter (nonprescription) drug for human use, primarily for the treatment of pinworms. FDA's Bureau of Drugs is currently studying gentian violet's use for this purpose.

#### FDA HAS NOT APPROVED THE USE OF GENTIAN VIOLET AS A FOOD ADDITIVE OR AS A NEW ANIMAL DRUG

FDA has not issued any regulations for the safe use of gentian violet as a food additive or as a new animal drug. The three firms in our review have submitted data in support of either FAPs or NADAs, but have not satisfied FDA's concerns about the safety of gentian violet. Also, according to FDA, gentian violet's utility as a mold inhibitor has not been adequately demonstrated.

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1/See page 10.



According to FDA, gentian violet is a suspected carcinogen whose safe use in veterinary products cannot be approved until certain testing requirements have been met. FDA maintains that further tests are required because of the proposed pattern of gentian violet use and the persistence of residues in the tissues of animals fed gentian violet. (See ch. 3.) These tests include:

- Metabolism tests that identify what compounds a substance breaks down to in the body, how fast and into which organs the components are dispersed, and how fast they are eliminated.
- Long-term chronic tests to measure the toxicological effects of gentian violet and its metabolites in experimental animals.

In addition, FDA officials believe it is necessary to develop a practical and fully validated method of analysis to monitor edible animal tissue to ensure that contaminated products will not enter the marketplace.

Although the three firms reviewed submitted tests intended to satisfy FDA requirements in these areas, FDA determined that the tests were inadequate to demonstrate the safety of gentian violet. (See ch. 3.)

The three firms submitted a number of studies to demonstrate the utility or effectiveness of gentian violet as a mold inhibitor in animal feed. However, the BVM official responsible for reviewing these studies advised us that the data submitted were inadequate to demonstrate the utility of gentian violet for this purpose. According to FDA, these studies suffered from one or more of the following deficiencies:

- Some studies were conducted in laboratories using a liquid as the medium for mold growth. According to FDA, studies must be conducted in animal feed. Although several studies were conducted using feed as a medium, FDA maintained that these studies suffered from poor experimental design and/or improper controls.
- Some studies showed variations in the effect of gentian violet on different types of mold. Such data would not support utility claims as broad as those proposed. The specific type of fungi inhibited at stated concentrations of gentian violet needed to be identified.

GENTIAN VIOLET NOT GENERALLY  
RECOGNIZED AS SAFE

The FD&C Act states that sponsors of substances that meet the statutory definition of general recognition of safety do not need to submit FAPs and NADAs for those substances. According to FDA, gentian violet does not qualify as a generally recognized as safe substance.

If a product is generally recognized as safe for use in animals by qualified experts, the product cannot be classified as a food additive or new animal drug and is not subject to premarketing clearance by FDA. FDA contends that the use of gentian violet in food-producing animals does not meet the test of general recognition of safety based on expert recognition. According to the FD&C Act (21 U.S.C. 321(s), (w)) and supporting case law, general recognition of safety must be based on:

- General recognition among qualified experts that its safety has been shown by scientific procedures under the conditions of its proposed use.
- Scientific procedures that form a supporting basis for such a showing.
- Evidence that any supporting basis that does exist is available to the community of qualified experts in general.

According to a BVM official, none of the firms involved in marketing gentian violet has been able to show the existence of any adequate and well-controlled studies that demonstrate safety. Therefore, gentian violet does not meet the necessary criteria to demonstrate general recognition of safety. The courts have agreed with this interpretation. (See United States v. Naremco, 553 F 2d 1138 (8th Cir. 1977); United States v. Dan-Mar, No. 78-08 G (U.S. Ga. Sept. 21, 1978).)

The FD&C Act also permits the status of substances added to food to be based on experience from "common use" of the product before January 1, 1958. FDA regulations interpreting this provision (21 CFR 570.30) state that qualified experts 1/

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1/Persons qualified by scientific training and experience to review scientific evidence and designate a substance as generally recognized as safe.

may base general recognition of safety for substances in use before these dates on a history of use without requiring the quality and quantity of scientific procedures needed for approval of a food additive regulation.

With regard to drugs used in animals, no comparable common use standard exists. However, a product can be prior sanctioned if it was marketed before June 25, 1938. According to BVM officials, there is no evidence that gentian violet was used as an animal drug before June 25, 1938, or as a food additive before January 1, 1958.

Although a product containing gentian violet was used as an animal drug before January 1, 1958, FDA maintains that this use does not qualify it for exemption from food additive status. The courts have also agreed with this interpretation. Gentian violet cannot be considered generally recognized as safe for use in food-producing animals based on its common use in food.

COURT DECISIONS SUPPORT  
FDA'S ASSESSMENT OF THE  
STATUS OF GENTIAN VIOLET

Before 1975, FDA took regulatory action against specific products that contained gentian violet. To preclude the continued marketing of any gentian violet products by two of the firms in our review, FDA sought judicial relief. In these two instances, FDA's assessment of gentian violet as a food additive and/or a new animal drug was upheld.

In April 1975, 1/ the United States brought suit to enjoin Naremcu from future interstate sale of any gentian violet products used as animal drugs or additives to animal feed until and unless premarketing approval was obtained from FDA. After a district court hearing, the Government was granted its request for a preliminary injunction covering all gentian violet products except GV-Eleven Medicated, a drug used to treat internal fungal diseases in poultry, and GV-Eleven Mold Inhibitor, a food additive used to prevent fungal growth in poultry feed. Both products contained 1.6 percent gentian violet as their sole active ingredient. On April 20, 1976, a permanent injunction was entered, which incorporated the provisions of the preliminary injunction.

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1/United States v. Naremcu, 553 F. 2d 1138 (8th Cir. 1977).

On February 16, 1977, the Government appealed the April 20, 1976, injunction, insofar as it permitted the continued marketing of GV-Eleven products and any other articles of food or drug containing gentian violet as their only functional ingredient.

On April 18, 1977, the U.S. Court of Appeals, Eighth Circuit, reversed the trial court's decision with regard to GV-Eleven Medicated and stated that:

"We have carefully reviewed the evidence offered to establish the general recognition among experts of the safety and effectiveness of gentian violet, the sole active ingredient in GV-Eleven Medicated. While the record contains some evidence that gentian violet is recognized by experts as safe, it lacks evidence of general expert recognition of gentian violet's effectiveness as an animal drug. \* \* \*

"\* \* \* the record here which lacks evidence of general recognition by experts of the effectiveness of gentian violet as an animal drug, compels the conclusion that gentian violet may not be marketed until a new animal drug application has been submitted and approved."

Although the court stated that the record contained some evidence that gentian violet was recognized by experts as safe, it did not reach a conclusion on the adequacy of this evidence to support general recognition of safety.

With regard to GV-Eleven Mold Inhibitor the court stated:

"A review of the evidence reveals that products containing gentian violet were added to poultry feed prior to January 1, 1958. The pre-1958 use of gentian violet in poultry feed was as an animal drug, however, not as a mold inhibitor or feed preservative. Naremco contends, and the trial court apparently agreed, that the addition of gentian violet to animal feed as a drug provided experience based on 'common use in food' prior to 1958 that experts could rely upon to recognize the safety of using gentian violet as a food additive. This contention neglects the vital difference between the use of a substance as a drug and as a food additive. When used as a drug to treat internal disorders,

gentian violet is fed to animals for sporadic and short periods of time. When used as a food additive to preserve feed, gentian violet is a constant factor in an animal's diet. Chronic ingestion of a substance differs significantly from short-term ingestion. \* \* \*

\* \* \* \* \*

"The record lacks evidence of pre-1958 use of gentian violet as a food additive or under conditions of long-term ingestion approximating use as a food additive. Nor is there evidence of scientific procedures \* \* \* upon which experts could base recognition of the safety of gentian violet as a food additive. The record is thus devoid of evidence probative of general expert recognition of the safety of gentian violet as a food additive and the trial court's finding that gentian violet has been shown to be generally recognized by experts as safe under the conditions of its intended use must be set aside as clearly erroneous."

In January 1978, 1/ FDA sought an injunction to enjoin Dan-Mar, from future interstate sale of gentian violet products used as new animal drugs or animal food additives unless and until premarket FDA approval was obtained. The firm had manufactured and shipped through interstate commerce an animal feed additive known as "Dye-Gen Mold Inhibitor" and an animal drug product known as "Dye-Gen Pink Eye and Blue Dressing Spray" ("Dye-Gen Pink Eye"). Gentian violet was an active ingredient in both products. The dispute was whether "Dye-Gen Mold Inhibitor" was a food additive and "Dye-Gen Pink Eye" was a new animal drug within the meaning of the act. Specifically, the issue was whether these products were generally recognized as safe and effective for use under the conditions prescribed, recommended, or suggested by their label. The firm claimed that its gentian violet products were, in fact, generally recognized as safe and/or effective for their intended uses.

On September 20, 1978, the court rendered its decision on the two products in question. It held that Dye-Gen Mold Inhibitor was not generally recognized among qualified experts

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1/United States v. Dan-Mar Enterprises, Inc., et al., U.S.D. Ct. N.D., Ga. Civil No. (C78-08G).

to be safe for use as an animal feed additive. Further, because different combinations of active ingredients may materially affect the safety of a feed additive, Dye-Gen Mold Inhibitor was not generally recognized as having been adequately shown, through experience based on common use in foods, to be safe for use as a feed additive.

In reference to Dye-Gen Pink Eye, the court held that it also was not generally recognized as being safe and effective for the uses under the conditions prescribed, recommended, or suggested by its label. Therefore, it held that Dye-Gen Pink Eye was a new animal drug within the meaning of the act. It in turn restrained the firm from distributing Dye-Gen Mold Inhibitor and Dye-Gen Pink Eye or any product containing gentian violet.

GENTIAN VIOLET IS NOT EXEMPT FROM  
THE PRECLEARANCE REQUIREMENT OF  
THE ACT DUE TO THE "GRANDFATHER"  
CLAUSE OF THE 1962 AMENDMENTS

Naremco claims that its gentian violet products should not be subject to the new animal drug and food additive pre-clearance requirements of the act based on a former FDA Commissioner's statement and the inclusion of a "grandfather" clause in the 1962 amendments to the act. The firm claims that its products were legally marketed before 1962 and, based on a Commissioner's statements, should be exempt from the need for NADAs and FAPs. The firm also claims that subsequent FDA regulatory actions against the firm's products were improper.

On the other hand, FDA maintains that:

- The statement by the former Commissioner in 1961 that certain products were "not new drugs" has no relevance to a determination by experts that, based on available scientific information, gentian violet is not generally recognized as safe for use in food producing animals, i.e., that it is a new animal drug and a food additive depending on its labeled use.
- The products referred to by the former Commissioner underwent labeling and formulation changes, thus making them new animal drugs.

Former FDA Commissioner's statement  
about the firm's products  
and the grandfather clause

In response to a request from a Member of Congress, a former FDA Commissioner, on April 13, 1961, indicated that several Naremco products, one of which contained gentian violet, were "not new drugs" but were in the category of drugs that may be distributed entirely on the firm's responsibility. But, the former Commissioner also expressed the opinion that Naremco had not provided adequate data to scientifically support many of the claims for the product containing gentian violet.

According to the firm, the former Commissioner's statement that its products were "not new drugs" would exempt those products from the effectiveness requirements of the 1962 amendments because of the grandfather clause contained therein.

Section 107(c)(4) of Public Law 87-781 (Oct. 10, 1962) added to the FD&C Act what has become known as the grandfather clause. Section 108(b)(3) of Public Law 90-399 (July 13, 1968) specifically identified animal drugs as being covered by the grandfather clause. Section 108(b)(3) of Public Law 90-399 states:

"In the case of any drug (other than a drug subject to section 512(n) of the basic Act as amended by this Act) intended for use in animals other than man which, on October 9, 1962, (A) was commercially used or sold in the United States, (B) was not a new drug as defined by section 201(p) of the basic Act as then in force, and (C) was not covered by an effective application under section 505 of that Act, the words effectiveness and "effective" contained in section 201(w) as added by this Act to the basic Act shall not apply to such drug when intended solely for use under conditions prescribed, recommended, or suggested in labeling with respect to such drug on that day."

Naremco believes its products meet these requirements since they were (1) on the market, since 1954, (2) "not new drugs" as stated in the former Commissioner's letter, and (3) not covered by any effective application under

section 505 of the act. The firm further contends that its products were not misbranded before the 1962 amendments since FDA, before the amendments, did not charge either the company or its products with misbranding. Therefore, based on the grandfather clause, the firm believes it was exempt from proving the effectiveness of its products and there is no need for it to submit either a FAP or a NADA.

FDA has disagreed with this reasoning. In an August 18, 1966, letter from FDA to the U.S. attorney in Tyler, Texas, the Assistant General Counsel commented on the firm's contentions as to the status of two of the firm's products, which were at that time the subject of seizure actions on the part of FDA. 1/

The U.S. attorney at Tyler, Texas, had requested FDA's views and recommendations on certain arguments raised by Naremco's attorney in the case regarding the firm's claim that its products should be regarded as "not new drugs" and, therefore, safe within the meaning of the act and also exempt from the preclearance requirements of the act. FDA's Assistant General Counsel stated:

"\* \* \* This argument cannot be supported in either fact or law. [The former Commissioner's] letter to [a Member of Congress] was not in reference to the same products which are now under seizure. The products to which the former Commissioner made reference in his letter, labels of which had been sent for comment to the Food and Drug Administration by the claimant, consisted of Naremco TSC 80 Veterinary, Naremco TSC 32, Naremco TSC Soluble, and a fourth labeled Naremco Ferro-Lac Poultry Formula. The TSC formulations contained as their sole active ingredient sodium phthalylsulfacetamide. \* \* \*. Although all of the seized articles with the exception of Myconox contain sodium phthalylsulfacetamide, it appears in combination with other active ingredients and chemicals and in none as the sole active ingredient. It is apparent, therefore, that the TSC products and those under seizure are not the same products.

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1/United States v. 41 Cases, More or Less, 420 F. 2d 1126 (5th Cir. 1970).



"The article labeled [Naremco's] Ferro-Lac Poultry Formula, the fourth product commented upon by [the former Commissioner], contained among other ingredients, sodium propionate, methylrosaniline chloride [gentian violet], and ferric choline, and was recommended for use in feeds for chickens and turkeys to reduce hemorrhagic symptoms resulting from Vitamin K deficiency. The only seized article which bears any similarity here, is labeled Myconox Medicated, containing the same ingredients as the Poultry Formula. However, the recommended uses are completely different. Whereas, the Poultry Formula was recommended for treatment of hemorrhagic symptoms, the article labeled Myconox is indicated for use in the treatment of mycosis."

\* \* \* \* \*

"Under 21 U.S.C. 321(p) a new drug is defined as one not generally recognized--as safe and effective for use under the conditions prescribed, recommended or suggested in the labeling thereof, \* \* \*.

"Any decision by the Food and Drug Administration on whether these products were new drugs, would, of necessity, have been based on the uses recommended or suggested in the labeling at that time. Inasmuch as the recommended or suggested uses considered by the Food and Drug Administration in 1961 are not the same as are now indicated for Myconox or any other seized article, the letter of [the Commissioner] can have no bearing on any aspect, including that of safety, of the seized products under their present uses.

"What has been said concerning the new drug aspects of the articles, also holds true for their food additive status. Under the definition contained in 21 U.S.C. 321(s), the intended use of a substance is the test by which a product is considered to be safe or unsafe. The intended use of the Poultry Formula is not the same as that of Myconox, and its status in 1961 is not determinative of its present status under a different intended use."

In addition, we believe that the following court cases involving Nareemco products that contained gentian violet establish that, without completed tests or investigations to determine the safety of animal drugs, the products never were generally recognized as safe for the uses intended and thus were new drugs excluded from the grandfather clause exemption.

United States v. 7 Cartons, More or Less \* \* \*  
Labeled in Part "FERRO-LAC SWINE FORMULA CONCENTRATE (MEDICATED)," 293 F. Supp. 660 (S.D. Illinois 1968), aff'd. 424 F. 2d 1364 (7th Cir. 1970) (government's affidavits supported position that there was a lack of general recognition that the product containing gentian violet seized by FDA had been demonstrated "through scientific procedures" to be safe under conditions of intended use); United States v. 41 Cases, More or Less, 420 F. 2d 1126 (5th Cir. 1970) (lack of general recognition of gentian violet as safe food additive pursuant to 21 U.S.C. 201(s)); United States v. \* \* \* 29 Bags FERRO-LAC Calf and Cattle Formula (Concentrate) Medicated, No. 70-02512 (D. Neb. Sept. 11, 1970) (FERRO-LAC is a new drug and is adulterated in that it contains unsafe food additives, including gentian violet); United States v. Articles of Food and Drug Coli-Trol 80 Medicated 372 F. Supp. 915 (N.D. Ga. 1974), aff'd. 518 F. 2d 743 (5th Cir. 1975) (combination including gentian violet adulterated within meaning of 21 U.S.C. 201(f,w), (w)(1), 304, 304(e), 402(a)(2)(c), and subject to condemnation in view of absence of general recognition based upon substantial scientific evidence of safety and effectiveness); United States v. 14 Cases, More or Less \* \* \* Labeled \* \* \*  
"NAREMCO MEDI-MATIC FREE CHOICE POULTRY FORMULA (Medicated) \* \* \*" 34 F. Supp. 922 (W.D. Mo. 1974) (drugs containing gentian violet were held to be "new animal drugs" because the absence of tests or investigations to determine the efficacy or safety of these drugs indicates they have never been generally recognized as safe or effective for the uses intended).

In United States v. 14 Cases, the court specifically considered the former Commissioner's statement and the applicability of Nareemco's products to the grandfather clause. The court stated:

"Having determined above that these are new animal drugs because of the absence of tests or investigations to determine the efficacy or safety of these drugs, we are of the opinion that these

drugs have never been generally recognized as safe and effective for the uses intended. We conclude, therefore, that the exemption is not applicable."

In other words, even though the former Commissioner may have recognized that gentian violet was used before 1962, this does not constitute general expert recognition in the sense required by the FD&C Act to prove that the product was "not a new drug," legally on the market at that time.

An FDA regulation issued in 1974 addressed similar circumstances surrounding other informal statements that a product is "not a new drug" or "no longer a new drug."

The regulation (21 CFR 310.100) states that:

"Over the years since 1938 the Food and Drug Administration has given informal advice to inquirers as to the new drug status of preparations. These drugs have sometimes been identified only by general statements of composition. Generally, such informal opinions were incorporated in letters that did not explicitly relate all of the necessary conditions and qualifications such as the quantitative formula for the drug and the conditions under which it was prescribed, recommended, or suggested. This has contributed to misunderstanding and misinterpretation of such opinions.

"For these reasons, all opinions previously given by the Food and Drug Administration to the effect that an article is 'not a new drug' or is 'no longer a new drug' are hereby revoked."

GENTIAN VIOLET DOES NOT QUALIFY FOR  
INTERIM FOOD ADDITIVE REGULATION

Two of the firms included in our review have submitted petitions requesting FDA to issue an interim food additive regulation for gentian violet as a mold inhibitor. FDA has determined that gentian violet does not meet the criteria for issuance of an interim food additive regulation.

The FD&C Act does not expressly provide for issuance of interim food additive regulations. Such regulations are authorized, however, by 21 CFR 180.1(a), which states:

"Substances having a history of use in food for human consumption or in food contact surfaces may at any time have their safety or functionality brought into question by new information that in itself is not conclusive. An interim food additive regulation for the use of any such substance may be promulgated in this subpart when new information raises a substantial question about the safety or functionality of the substance but there is a reasonable certainty that the substance is not harmful and that no harm to the public health will result from the continued use of the substance for a limited period of time while the question raised is being resolved by further study."

When FDA first proposed this regulation, it indicated that an interim food additive regulation would apply only in limited circumstances. In that proposal (37 Federal Register 6207 (Mar. 25, 1972)), the FDA Commissioner stated that an interim regulation might be justified in the case of a regulated food additive (i.e., one whose use had been permitted under provision of a food additive regulation). The stated purpose of the proposed regulation was to allow continued use of a substance about which new questions concerning safety or functionality had been raised, pending completion of new studies, provided there was reasonable certainty that the substance was not harmful.

On November 16, 1977, representatives of Naremco met with officials of FDA's BVM, Bureau of Foods, and General Counsel. According to the memorandum of conference prepared by FDA, a Naremco official asked whether FDA could grant an interim food additive approval for the use of gentian violet. This official indicated that, if FDA would provide such an approval, the firm would agree to perform any tests of any duration required by FDA. The FDA officials stated that, because gentian violet had never been approved for feed use, it would be in a different category than other chemicals for which interim food additive regulations were requested.

On December 1, 1977, Naremco requested that FDA issue an interim food additive regulation for the use of gentian violet as a mold inhibitor in poultry feed. In a February 9, 1978, letter from the Associate Commissioner for Compliance, FDA advised the firm that it would be inappropriate to issue this interim regulation.

On December 21, 1977, Dan-Mar petitioned for an interim food additive regulation for the use of gentian violet as a fungistat in feed for broiler and broiler breeder chickens. In a January 11, 1978, letter from the Acting Associate Commissioner for Compliance, Dan-Mar was advised that FDA had concluded that it would not be appropriate to issue an interim food additive regulation for gentian violet.

According to the Acting Associate Commissioner for Compliance:

"The FDA's consistent position has been that an interim food additive regulation is appropriate only for a substance that has enjoyed an agency sanction, either as generally recognized as safe or as a regulated food additive. Stated another way, the agency will not authorize the use of a food additive under an interim food additive regulation if the substance in question has not previously been used--for the purpose at issue--in a lawful manner over a substantial period of time.

"Considering the foregoing, gentian violet for use as an animal food additive could not qualify for an interim food additive regulation. There is no existing food additive regulation permitting use of gentian violet in animal feed. The FDA for a number of years has considered gentian violet to be an unapproved food additive within the meaning of Sections 201(s) and 409 of the Act. In fact, the Eighth Circuit Court of Appeals has recently held that gentian violet is not generally recognized as safe for use in animal feed. See United States v. Naremco, Inc., 553 F. 2d 1138 (8th Cir. 1977)."

On February 13, 1978, Dan-Mar submitted a petition requesting that FDA reconsider its January 11, 1978, decision denying the firm's interim FAP. According to Dan-Mar, FDA's decision was incorrect because:

--The decision failed to take into account the critical need for continued availability of gentian violet to prevent the outgrowth of aflatoxin in poultry feed. The firm contended that FDA's decision ignored an immediate and serious public health problem by relying on narrow legal technicalities and on an unspecified remote and conjectural possibility of harm from the firm's proposed use of gentian violet.

- The requirement of a prior agency sanction is inconsistent with previous statements by FDA of its policy on interim food additive regulations. These statements indicate that interim food additive status should be available to substances not subject to a prior agency sanction and that interim food additive regulation is appropriate when the main weight of scientific evidence supports safety, which is certainly the case with gentian violet.
- There was no demonstrable or identifiable harm to the public health presented by the proposed interim food additive regulation for gentian violet.
- There was an immediate and widespread need for a substance to control mold growth in animal feed.
- There were considerable data supporting the safety and efficacy of gentian violet as a fungistat.
- There was no substitute for gentian violet capable of providing equivalent mold control.

Dan-Mar concluded that the granting of an interim food additive regulation was in, rather than against, the public interest. The firm said that when the overwhelming need for gentian violet to control aflatoxin 1/ was taken into consideration the denial of this petition was clearly erroneous and should be reconsidered.

FDA's Associate Commissioner for Compliance, in an April 4, 1978, letter, responded to the firm's petition for reconsideration of the interim food additive regulation. He stated that:

"\* \* \* we have reviewed the petition and are denying reconsideration \* \* \*.

"The one new matter raised in the petition for reconsideration has to do with the interpretation of the preamble published in the Federal Register of March 25, 1972. We are of the opinion that a fair reading of the applicable paragraphs of that preamble leads to the conclusion that the sentence in the January 11, 1978, letter of denial, that 'an interim food

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1/See page 31.

additive regulation is appropriate only for a substance that has enjoyed an agency sanction, either as generally recognized as safe or as a regulated food additive' is correct."

The Associate Commissioner indicated that FDA remained convinced that an interim food additive regulation was not appropriate where there had been both an administrative and a judicial determination that a substance was not generally recognized as safe. He indicated further that FDA did not believe that the public interest would be served by any attempt to promulgate an interim food additive regulation under such circumstances. He concluded that the petition would not be reconsidered.

In a November 6, 1978, memorandum to the Commissioner, FDA's Chief Counsel commented on the possibility of interim food additive status for gentian violet as a mold inhibitor in animal feed. He stated that:

"After studying this question, I have concluded that FDA regulations do not permit the issuance of an interim food additive regulation for use of gentian violet for any purpose."

The Chief Counsel felt the lawful uses within the scope of section 180.1(a) were as a generally recognized as safe substance and as an approved food additive (i.e., pursuant to a food additive regulation). He indicated that gentian violet did not have a history of use as a generally recognized as safe substance or as an approved food additive. Consequently, it was not eligible for an interim food additive regulation.

The Chief Counsel stated:

"21 CFR 180.1(b) provides an additional and independent obstacle to the issuance of an interim food additive regulation for gentian violet:

'No interim food additive regulation may be promulgated \* \* \* if there is a reasonable likelihood that the substance is harmful or that continued use of the substance will result in harm to the public health.'

He further indicated that it had been FDA's scientific judgment that there was a reasonable likelihood that gentian

violet was carcinogenic and otherwise harmful and, therefore, a reasonable likelihood that its use would result in harm to the public health. He cited United States v. Dan-Mar Enterprises, Inc., Civ. No. C78-08G (N.D. Ga. Sept. 21, 1978), in which the court made the following findings:

- Gentian violet is a suspected carcinogen, a probable mutagen, and a potent clastogen. When ingested by roosters as a feed additive, it has an unexplained effect on fertility.
- When it is ingested by chickens as a feed additive, residues of gentian violet are absorbed and remain in edible chicken tissues. If such edible chicken tissues are consumed by humans, the residues are introduced into the human body.
- Residue studies evaluating the effects of gentian violet have been conducted; however, residue data cannot be properly evaluated without an adequate toxicity base. No such data base exists for gentian violet.
- Lifetime chronic multigenerational toxicity studies in rodents and poultry appear to be necessary to resolve the safety concerns surrounding the use of gentian violet in animal feed. No such studies have been conducted for gentian violet.

Based on this information, the General Counsel concluded that gentian violet was within the prohibition of section 180.1(b) and, therefore, not eligible for an interim food additive regulation.

BUREAU OF DRUGS POSITION REGARDING  
AVAILABILITY OF GENTIAN VIOLET  
AS AN OVER-THE-COUNTER DRUG

Officials of all three firms indicated that they felt FDA was being unfair in its refusal to allow the sale of gentian violet as an animal drug or food additive in view of gentian violet's current use in human medicine.

The Deputy Director of FDA's Bureau of Drugs said that gentian violet was used in human drug products as an anthelmintic for the treatment of pinworm infestations and as a topical and vaginal antiinfective agent. FDA told us that the drug was largely outmoded by antibiotics and systemic



antibacterial drugs, not so much because of its inefficacy, but because the newer anthelmintics are safer and more effective. Gentian violet has also been used in treating burns to control infection, but it is used very little for this purpose today.

Within FDA's Bureau of Drugs, the Over-the-Counter Drug Evaluation Division has responsibility for regulating the use of gentian violet in human medicine. The director of this division said that, while there are no approved new drug applications for gentian violet, it has been considered an old drug which has been effective in human medicine. The director told us that the Bureau of Drugs is aware of concerns over the safety of gentian violet. He said that there is a significant difference between the use of gentian violet in humans and animals. For instance, in human use, a small portion of the population is exposed to a high dose for a short time, while in animal use, a major portion of the population is, or can be, exposed to a small dose for an indefinite period. The body tends to eliminate a large short-term dose more efficiently than a small long-term dose. The director also stated that in human medicine a risk-benefit assessment may be taken into consideration. In other words, does potential benefit outweigh the potential risk? In veterinary medicine, a risk-benefit assessment cannot be applied to the consideration of the human food safety issues arising from the use of the compound.

Bureau of Drugs review panel's  
assessment of gentian violet

Since 1962, FDA has reviewed human drugs for effectiveness as well as safety. During the 1960s this review concentrated on prescription drugs. In 1972, FDA initiated reviews of active ingredients used in nonprescription (over-the-counter) drugs. FDA established advisory panels made up of experts who reviewed all available evidence to determine if active ingredients were safe and effective for their intended use. The panels were not required to review individually the more than 300,000 drugs being sold but rather to review the approximately 800 active ingredients in these products.

The panels were then to recommend into which of the following categories each active ingredient should be placed.

Category I - Safe and effective as intended.

Category II - Not safe and effective as intended.

Category III - Not enough information is available to make a determination. 1/

The panels were to prepare reports containing their findings on active ingredients used in broad product categories. The resulting findings are strictly advisory and not binding on FDA. Each report is published in the Federal Register along with a preamble containing FDA's opinion of the active ingredient and a proposed monograph describing how FDA plans to regulate a particular active ingredient. FDA invites public comments on this information. Following evaluation of these comments, FDA publishes a tentative final monograph for public comment. After FDA reviews all data submitted, it publishes a final monograph that sets standards specifying ingredients and labeling so that a product complying with these standards may be marketed without any agency preclearance.

An advisory panel reviewed data available for gentian violet and concluded, in an October 1978 report, that gentian violet was safe and effective as a human drug when used as specified in its report. The panel recognized, however, that questions concerning the safety of gentian violet existed. The panel stated in its report:

"The Panel is aware of the recent concern that gentian violet may be a carcinogen and of the recently published and unpublished data regarding its potential carcinogenicity. The Panel recognizes the propriety of the FDA Bureau of Foods' position that the present weight of the evidence regarding the toxicity of gentian violet indicates that gentian violet may be carcinogenic and that the question of carcinogenicity cannot be unequivocally answered based on the available data. No decision on the safety of gentian

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1/In the May 13, 1980, Federal Register (Vol. 45, No. 94, p. 31422), FDA published a proposed revision of its regulations for reviewing and classifying over-the-counter drugs to delete the provision that authorizes the marketing of a Category III ingredient or other condition in such drug products after a final monograph.

violet residues in the edible parts of animals can be made until appropriate data resolving the question of carcinogenicity are submitted to the FDA.

"The Panel recognizes that safety considerations regarding the short-term use of a compound as a drug in humans differ significantly from safety considerations regarding low-level, long-term human exposure to that compound in food. In this context, the data regarding the potential carcinogenicity of gentian violet remain of concern, but do not preclude the short-term effective use of gentian violet as an anthelmintic in humans. The Panel recommends that further testing resolving the carcinogenic concerns associated with gentian violet be performed. Since there is no conclusive proof that gentian violet is a carcinogen, the Panel concludes that it is safe for OTC [over-the-counter] use as an anthelmintic when used as directed."

The director, Over-the-Counter Drug Evaluation Division, said that the division reviewed the panel's report and is considering the panel's recommendation that gentian violet is generally recognized as safe and effective and should continue to be available as an over-the-counter anthelmintic. The Bureau of Drugs may agree or disagree with the panel's recommendation. If it should disagree, the reasons will be incorporated into the preamble and proposed monograph for publication in the Federal Register.

### CHAPTER 3

#### SAFETY AND EFFECTIVENESS

##### OF GENTIAN VIOLET NOT DEMONSTRATED

The safety and effectiveness of gentian violet as a food additive or new animal drug have not been demonstrated to FDA's satisfaction. FDA has determined that the reports of tests submitted by the three firms do not demonstrate that gentian violet, when used as an animal drug or food additive, will be safe to humans consuming food from animals fed the substance. In addition, studies submitted by the firms do not demonstrate that gentian violet is effective as a mold inhibitor. Although all of the firms have indicated that they disagree with FDA's interpretation of the data submitted and with the need for long-term tests, none has used the legal procedures established to settle such disputes.

##### SAFETY OF GENTIAN VIOLET AS AN ANIMAL DRUG OR FOOD ADDITIVE NOT DEMONSTRATED

In March 1975, a Bureau of Foods petition reviewer became aware of the carcinogenicity of a dye structurally related to gentian violet and determined that gentian violet was a suspect carcinogen. As a result of that determination and other information submitted by the firms or otherwise identified by FDA, FDA has determined that the safety of gentian violet, as a food additive or new animal drug, cannot be established without lifetime chronic toxicity tests with in-utero exposure, preferably in rats and mice. The need for long-term studies was based on three factors: (1) suspected carcinogenicity of gentian violet, (2) persistence of residues in tissues of animals fed gentian violet, and (3) pattern of use of gentian violet.

##### Studies needed to establish safety

Before March 1975, FDA had advised the three firms that the following studies were necessary to establish the safety for humans from food of animals of gentian violet:

- Two 90-day oral toxicity studies. (One each using rats and dogs.)

- A complete metabolism study in the target animal. (This study must measure the quantity of gentian violet and/or its metabolites in tissues. Further, the identity of each metabolite should be established.)
- An adequate tissue residue assay method. (Validated in tissues and of sufficient sensitivity to determine minimal residues of gentian violet and/or its metabolites.)

In May and June 1975, the three firms were advised that the studies required by FDA to demonstrate the safety of gentian violet had changed and the following studies would be required:

- A chronic multigeneration study in a rodent, preferably the rat.
- A lifetime study with in-utero exposure in mice.
- A tissue residue depletion and metabolism study.

Lifetime studies in rats and mice are generally recognized as 2-year studies. This includes only the time required for feeding prepared diets to the test animals. Additional time is required to develop protocols for the studies, establish the levels of test feeding substances, prepare and analyze tissue slides, and report on the findings of the studies. The entire process could take 4 or more years. None of the firms has submitted to FDA results of tests that would satisfy these requirements.

Basis for concern that gentian violet may be a carcinogen

The Chairperson of the Bureau of Foods' Cancer Assessment Committee 1/ told us that gentian violet is structurally related to several known carcinogens, including pararosanine pamoate and Food, Drug, & Cosmetic Violet #1. All three of these substances belong to a class of dyes known as aminophenylmethanes. And, according to FDA's Bureau of Foods, the chemical structure and biological activity of a substance has some predictive value in determining if long-term studies are required to assess safety.

A Bureau of Foods, Division of Toxicology, veterinarian responsible for reviewing toxicological studies of gentian violet said that, in March 1975, a pharmacologist in FDA's Bureau of Drugs advised him that pararosanine pamoate was a carcinogenic agent. The pharmacologist also indicated that he had become aware of the petitions for use of gentian violet during a February 25, 1975, telephone conversation with an official of Naremco. According to a memorandum of this conversation, the Naremco official called to discuss the development of safety data for the use of gentian violet in human medicine. The Bureau of Drugs pharmacologist advised the Naremco official that he would be happy to comment on studies being performed by the firm but that there might be a question of possible carcinogenicity since a related compound had been found to be carcinogenic. A copy of this memorandum was provided to the Bureau of Foods.

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1/The Bureau of Foods' Cancer Assessment Committee was established in January 1978 to ensure (1) a uniform and consistent scientific approach for dealing with diverse problems of carcinogenicity, (2) that all aspects of data on carcinogenicity are provided interdisciplinary review encompassing considerations of the pertinent toxicology, pathology, statistics, chemistry, epidemiology, and other disciplines as appropriate, and (3) that the highly specialized and complex issues of carcinogenicity are addressed in a manner reflecting a full understanding of the issues involved. The Committee, on May 18, 1978, considered the potential for carcinogenicity of gentian violet.

Additionally, in a March 30, 1979, notice published in the Federal Register (44 Federal Register 19035), FDA commented:

"Additional concerns regarding the carcinogenicity of gentian violet arise from its chemical structure. Crystal violet, a main component of gentian violet, belongs to a class of dyes related by molecular structure, which can be generally referred to as aminophenylmethanes. A few of these are known animal carcinogens and two, auramine and magenta, have been implicated as human carcinogens as a result of observations of human exposure in the dye industry."

Gentian violet has also been shown to produce adverse effects on genetic 1/ material. FDA's Bureau of Foods, in a March 10, 1978, review of the safety of gentian violet residues in edible animal tissues resulting from veterinary use, commented on three reports 2/ which showed that gentian violet may be mutagenic 3/ and carcinogenic. According to FDA, these reports describe studies in which gentian violet exhibited adverse effects on genetic material similar to the effects of known mutagens. According to the Bureau of Foods, these studies show that gentian violet is capable of causing damage to deoxyribonucleic acid, chromosome breakage and

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1/Pertaining to heredity and variation of organisms and the mechanisms which affect them.

2/"Possible Hazard in the Use of Gentian Violet," Rosenkrantz and Carr British Medical Journal (Sept. 18, 1971, p. 702).

"Cytogenetic Assays of Chemical Clastogens Using Mammalian Cells in Culture," Hsu, T.C., et al., Mutation Research, 45: 233-247, 1977.

"Cytogenetic Study of the Genetic Toxicity of Gentian Violet," Au, W., Pathak, S., Collie, C.J., and Hsu, T.C., Mutation Research, 58: 269-276, 1978.

3/A mutation is any heritable change, such as a chemical transformation of an individual gene, that may alter the functions of, rearrange the structure of, or cause the gain or loss of parts of a chromosome.

rearrangements, as well as mitotic (a type of cell division) abnormalities in in-vitro experiments. The Bureau of Foods indicated that such effects are commonly found with chemicals that cause other mutagenic effects. The Bureau of Foods also stated that, by inference, gentian violet may also have the potential to produce mutagenic and carcinogenic effects.

A 2-year study of rats fed gentian violet was conducted by an FDA employee from 1949-51. A Bureau of Foods petition reviewer commented on this study in a February 26, 1976, memorandum to BVM and indicated that the results reported involved gross pathological observations of the lungs, liver, kidney, gonads, spleen, and other organs and tissues. According to the Bureau of Foods official, liver lesions consisting of tumors and other changes in the treated groups were found. The highest preponderance of liver lesions were noted in animals fed the two highest concentrations of gentian violet. The study also showed there were more tumors for the treated groups than the control group. The petition reviewer stated that:

"These data are not of the quality we prefer for carcinogenicity screening studies. The number of animals used were too few and the data lack many details. The results from this study are not adequate to show that gentian violet is not carcinogenic. Rather, they lend support to our request for further data on this question. Therefore, we are still of the opinion that gentian violet has to be tested adequately to demonstrate non-carcinogenicity \* \* \*."

The director, Division of Pathology, Bureau of Foods, reviewed the tissue slides taken from animals in this test. In a February 1, 1978, memorandum to the assistant to the Bureau director for scientific policy, the director, Division of Pathology, stated that there were a number of deficiencies in the study when considered from the viewpoint of current requirements for carcinogenicity testing. These included the small numbers of animals per group starting the experiment and examined histopathologically; the lack of a methodical plan for sampling tissues from necropsied animals; and the poor quality of microscopic sections which made refined diagnoses more difficult. The director also stated that, despite the deficiencies mentioned which could cast doubt on the validity of negative findings, positive findings



could be accepted since they would not be invalidated by the deficiencies. The director also stated that:

"\* \* \* The lesions described are not cancerous or clearly pre-cancerous but represent neoplastic-type alterations which are interpreted as qualitatively in the direction of cancer.

"Despite a number of significant deficiencies in the design and execution of the study, the positive observations contained in this report are not obviated by the deficiencies.

"Therefore, it cannot be concluded that the chronic feeding of gentian violet to rats is innocuous since dose-related neoplastic-type proliferations were observed in their livers. The precise relationship of the lesions with respect to carcinogenesis will require further study to elucidate."

#### Pattern of exposure by humans

In a March 10, 1978, review, the Bureau of Foods commented on the results of tissue residue and metabolism studies submitted by the firms in our review. According to the Bureau of Foods, while these tests could only be considered preliminary, the major conclusion drawn was that there was a relatively high probability that chronic human exposure would result from the use of gentian violet in food-producing animals. The Bureau stated that, while the available data did not adequately identify the residues (gentian violet or a metabolite), the data strongly indicated that additional tests, including long-term tests, were needed to establish safe conditions of use of gentian violet.

#### Use characteristics of gentian violet

According to the Bureau of Foods, the manner in which a substance is used is a factor to be considered in determining the types of studies needed to establish safety. The Bureau believes that on the basis of the recommended concentrations of gentian violet in the diet of animals fed the substance, there is a high potential for extensive and chronic exposure to residues in edible tissue. For this reason, the Bureau believes long-term studies are needed.

LONG-TERM STUDIES OF GENTIAN  
VIOLET BEING CONDUCTED BY FDA

FDA has initiated a long-term study of gentian violet at its National Center for Toxicological Research (NCTR). <sup>1/</sup> The objective of the study is to provide oncogenic, teratogenic, and toxicological data for gentian violet. FDA estimates the study will be completed about May 1983.

In a September 20, 1978, memorandum to the BVM director, the acting director, Division of Drugs for Avian Species, proposed that FDA conduct tests of gentian violet at NCTR. The acting director stated that four sponsors had petitions before FDA requesting the use of gentian violet in poultry feed as either a drug or food additive. The biggest obstacle to approval of these petitions was the question of human safety, in particular the need for long-term testing of gentian violet. The acting director stated that he viewed long-term testing of gentian violet as a potential NCTR project.

In a meeting between the FDA Commissioner and BVM on October 10, 1978, a decision was made to have FDA pursue long-term testing of gentian violet. In an October 23, 1978, memorandum, the director, Bureau of Foods, notified the BVM director that the Bureau of Foods would participate in designing gentian violet studies to be conducted at NCTR. The final protocol for the testing of gentian violet was completed in August 1979. This protocol was developed by officials of FDA's Bureau of Foods, BVM, and NCTR. According to this protocol, the following specific studies will be conducted:

- Metabolism in chickens, mice, and rats.
- Maximum tolerated dosage in mice and rats.
- Teratology in rats.

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<sup>1/</sup>NCTR was established in January 1971 to examine the biological effects of a number of chemical substances, such as pesticides, food additives, and therapeutic drugs. NCTR undertakes studies aimed at understanding dose-response relationships for long exposures to low doses of chemicals.

--Chronic lifetime in rats and mice and multigeneration reproduction in rats.

As of March 1980, the maximum-tolerated-dosage feeding study had been conducted. Based on the results of this study, FDA will determine the levels of gentian violet to be included in the diets of test animals for the other studies. A Bureau of Foods official participating in the study told us that the lifetime rat and mice studies were initiated in May 1980 and should be completed about May 1982. The examination of test animals, analysis of test data, and preparation of a report should take an additional 9 to 12 months.

EFFECTIVENESS OF GENTIAN VIOLET  
AS A MOLD INHIBITOR IN ANIMAL  
FEEDS NOT DEMONSTRATED

Two firms--Dan-Mar and Naremco--have submitted data designed to show that gentian violet is effective in inhibiting the growth of molds in animal feeds. According to FDA, these data contain a number of deficiencies that preclude their acceptance. Officials of the third firm reviewed said that, based on tests they had performed, they had concluded that gentian violet was not effective against molds in animal feeds. They believe that gentian violet has a therapeutic effect against certain disease conditions in poultry.

When sold as a mold inhibitor, gentian violet is a food additive as defined by the FD&C Act. The act states that a food additive is a substance whose intended use may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food. FDA regulations require that food additives must be shown to have the physical or other technical effect intended.

Need for mold inhibitor in animal feeds

Molds grow on grain, forage, or other animal feedstuffs and are important because of the potentially toxic substances they produce. These molds may produce mycotoxins 1/ that

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1/Mycotoxins are fungal or bacterial toxins that may cause a disease called Mycotoxicosis, which results in liver injury; abortion; production of weak, small offspring; abnormal bleeding; excessive salivation; gangrene or other disease signs; or animal death.

can cause economic loss due to reduced growth rate as well as animal disease and death. Aflatoxins, the mycotoxin with the greatest potential harmful effect, are metabolites of the mold Aspergillus flavus. Aflatoxins are extremely toxic and have been found to be carcinogenic in a number of animal species.

Mycotoxins may be formed either at harvest or other times when high humidity or high moisture content in the feedstuffs favor mold growth. According to Dan-Mar and Naremco, the use of gentian violet products at the recommended levels can inhibit the growth or propagation of molds in animal feeds and, thus, inhibit the development of harmful mycotoxins.

FDA's evaluation of data  
submitted by the firms

According to a BVM petition reviewer, the data submitted by Dan-Mar and Naremco to demonstrate that gentian violet can inhibit the growth of mold contain a number of deficiencies. To illustrate:

- Several tests were conducted under laboratory conditions. According to FDA, these tests are not acceptable to demonstrate that gentian violet will have the claimed effect in actual use in animal feeds. Tests must be conducted under conditions of expected usage.
- Tests that were conducted in feed were not conclusive in demonstrating the effectiveness of gentian violet.
- The type of molds against which gentian violet is effective and the degree of inhibition were not specified.

On December 1, 1977, Naremco submitted a request for an interim food additive regulation. (See p. 15.) Naremco, in support of this request, submitted data intended to demonstrate the effectiveness of gentian violet in inhibiting mold in animal feeds. An additional study was submitted by Naremco on December 7, 1977.

FDA's Associate Commissioner for Compliance, in an April 9, 1978, letter to Naremco, commented on the effectiveness data submitted. The Associate Commissioner stated:

- The studies reported in this submission concerning the inhibitory effects of gentian violet on *Aspergilli* and the biosynthesis of aflatoxins are not appropriate to support the claim of utility in poultry feeds. These studies were conducted using liquid media as the medium for fungal growth. The utility of gentian violet must be demonstrated in feed.
- The data from studies conducted with *Aspergilli* in liquid media indicated considerable variation between strains with respect to sensitivity to gentian violet. These data would not support a utility claim as broad in scope as the one proposed. Specific fungi inhibited by the concentration of gentian violet intended for use would have to be justified.
- One strain of *Aspergillus parasiticus* became more resistant to gentian violet with repeated exposure to the dye. This response must be investigated further in order to assess its impact with respect to potential mycotoxin synthesis.
- Three studies that were conducted using feed as the substrate did not provide adequate information to support the utility claim due to poor experimental design and/or improper control. Two of these reports did not contain raw data.
- The term inhibit should be defined precisely as it applies to fungal growth. It is our opinion that inhibit means to prevent or eliminate fungal growth and mycotoxin biosynthesis. If it is your contention that inhibit means to retard fungal growth and synthesis of the toxins, then the amount of retardation should be quantified.

On July 1 and December 21, 1977, Dan-Mar submitted data designed to demonstrate the effectiveness of its gentian violet product as a mold inhibitor. The July 1 submission was in support of a food additive petition. The December 21 submission was in support of an interim food additive regulation. In a June 2, 1978, letter from the Associate Commissioner for Compliance, FDA advised the firm of its evaluation of the submitted data. The Associate Commissioner stated that the data were inadequate to support approval of the firm's product in animal feeds. Some of the deficiencies identified were:

- Most of the studies conducted under laboratory conditions did not use animal feeds as the medium for mold growth.
- Some studies showed that considerable variation existed between strains of one type of mold with respect to sensitivity to gentian violet.
- In one study, the effects of crystal violet (a component of gentian violet) on mold growth were tested. The results of this study did not support the firm's claim because (1) crystal violet was applied in a solution and not as a dry ingredient as would be the case with feed and (2) the concentrations at which crystal violet was added were 2.5 to 5 times the proposed use level.

In a January 24, 1978, review of the effectiveness of gentian violet as a mold inhibitor in feed, a BVM official concluded that

"As of this date, not one adequately designed and conducted experiment, concerning the effectiveness of gentian violet in feed, has been submitted to BVM for review. There is no question that gentian violet in solution [inhibits mold] depending on the organism and the concentration of the dye. This is especially true when it is applied directly to the site of [mold]. Considerable doubt remains however concerning its effectiveness as a [mold inhibitor] in feed particularly at the current proposed concentrations.

"It is our opinion that the current claim of utility for gentian violet is too general and lacks definition. It should specify the [mold] which can effectively be inhibited by gentian violet at the proposed use levels. The terms [label claims] as used by the firms should be defined. The claims should also be supported by data collected from properly designed and conducted experiments using feed as the substrate for [mold] growth."

ADMINISTRATIVE HEARING PROCEDURES  
NOT USED BY FIRMS

All three of the firms in our review have disagreed with FDA's assessment of the adequacy of safety and/or effectiveness data and also with the need for long-term tests to determine the safety of gentian violet in veterinary medicine. However, none of the firms used the administrative procedures provided by the act or FDA's regulations to resolve disputes over FDA rulings denying NADAs and FAPs submitted by the firms.

NADAs

The FD&C Act provides that, if FDA finds a NADA not approvable, the sponsor shall be given an opportunity for a hearing. If the sponsor submits a request for a hearing and supporting information and analysis to raise a genuine and substantial issue of fact, a hearing before an administrative law judge will be conducted. If no such issue of fact is established, the agency may deny, by order, the request for a hearing. If a hearing is granted, the administrative law judge makes an initial decision, reviewable by the Commissioner. If the Commissioner finds that the safety and effectiveness of the new animal drug has not been demonstrated, then he shall issue an order refusing to approve the application. The act further states that an applicant may appeal an FDA order refusing approval of an application. Such appeal shall be taken by filing in the proper U.S. court of appeals a written petition that the order be set aside. The judgment of the court affirming or setting aside any such order shall be final, subject to review by the U.S. Supreme Court.

FAPs

The act provides that, if FDA denies approval of a FAP, any person adversely affected may file an objection requesting a public hearing. The procedures for new animal drug applications also apply to food additives.

If any adversely affected person disagrees with any order resulting from a hearing, that person, like a new drug applicant, may petition the U.S. court of appeals. The petition may request that the entire order, or any part, be set aside. The judgment of the court shall be final, subject to review by the Supreme Court.

### Firms have not used appeal procedures

None of the firms in our review have used the appeal procedures established by the act and FDA regulations. Dan-Mar told us that it had not used the appeal procedures because it felt that such an approach would be unsuccessful. The firm believed that FDA had reached a decision that gentian violet would not be allowed on the market without long-term tests and any further appeals would be futile. AHP stated that the cost of filing an appeal was prohibitive. Naremco said that it had not used the appeal procedures because, even though it had submitted data in support of gentian violet's safety and efficacy, it had never submitted a FAP or NADA.

In June 1965, Naremco did submit an application to request approval of an additional claim for a product the firm believed was legally on the market. When FDA claimed that the product itself was a new drug and required preclearance, the firm withdrew the application. Thus, Naremco had no basis on which to file an appeal. Officials of the firm told us that they did not submit a FAP or NADA because, from 1965-77, they were in the courts almost constantly trying to prove that gentian violet was generally recognized as a safe food additive that had been legally marketed as a new drug and, therefore, was exempt from the need for such requirements. According to these officials, Naremco's attorney had advised against filing such a petition and/or application because to have done so would have been an admission that the firm's products were not exempt from such requirements.

### CONCLUSIONS

FDA has determined that the safety of gentian violet cannot be established without long-term tests designed to assess whether it is carcinogenic. The tests submitted by the three firms have not satisfied this requirement. Likewise, none of the firms submitted data that adequately demonstrate to FDA's satisfaction that gentian violet will have utility as a mold inhibitor in animal feeds. Although each of the firms has disputed FDA's evaluation of safety data and the need for additional testing, none of the firms have used established appeal procedures to resolve such disputes. In our opinion, the position taken by FDA concerning the safety and utility of gentian violet is reasonable based on the reviews of BVM and the Bureau of Foods.



## CHAPTER 4

### REGULATORY ACTIONS TAKEN BY FDA

FDA is responsible for ensuring that all animal drugs and animal food additives are safe and effective. In this regard, FDA has taken regulatory action against each of the firms in our review. Two of these firms have indicated that FDA's actions toward them and their products have been unreasonable. However, based on our review, we believe that FDA has acted within the bounds of its regulations and legislation. It should also be noted that, in 9 of 10 cases involving products which contain gentian violet, FDA's actions have been supported by Federal courts.

### TYPES OF REGULATORY ACTIONS TAKEN BY FDA

The regulatory actions available to FDA include (1) inspections, (2) adverse findings/warning letters, (3) regulatory letters, (4) product seizures, and (5) injunctions and criminal prosecution. FDA officials told us that they attempt to get firms to cooperate voluntarily through persuasion rather than formal regulatory actions. When appropriate, FDA informally notifies the firms that marketing certain products is considered to be in violation of the act and requests that corrective action be taken. If this fails, FDA takes formal regulatory action.

The FD&C Act states that firms marketing substances subject to the act be inspected at least once every 2 years. More frequent inspections may be made if FDA determines that they are needed. Inspections are conducted by FDA's district offices. These inspections may be comprehensive (including all substances regulated and all aspects of that regulation, i.e., good manufacturing practices, labeling, etc.) or directed at one or more specific items or practices of the firm. Upon completion of the inspection, a written report is prepared. The report contains specific information on:

- Purpose of the inspection.
- History of the firm's business.
- Persons interviewed and their responsibilities.
- Products handled.
- Present operations, raw materials, and manufacturing processes.

- Formulas, labels, coding, and controls.
- Distribution and shipments.
- Cited violations.
- Discussion with management.
- Conclusions from the overall inspection.

If FDA identifies a violation of the act, it sends the firm an adverse finding or warning letter. This letter identifies the violation and directs the firm to correct the problem.

Later, if the firm does not correct the deficiencies noted, FDA may issue a regulatory letter. This letter will inform the firm that it has 10 days to respond or show cause why no further regulatory action should take place.

If the firm does not respond adequately to the regulatory letter, FDA may initiate seizure action against the product, seek an injunction to require the firm to correct the problem or to stop carrying on the activities to which FDA objects, or seek prosecution of the firm.

The basis for seizure is a recommendation letter to BVM from the FDA district office that conducts the inspection. The recommendation usually contains information regarding (1) the date the sample was collected, (2) the person who collected the sample, (3) the product sampled, (4) the manufacturer, (5) the person who requested the sample, (6) the reason for and results of the sampling, and (7) the reason why seizure was recommended. In some instances, a seizure may be disapproved because of (1) lack of sufficient data, (2) inadequate sample collection, and (3) pending litigation.

FDA generally initiates seizure actions by filing a complaint in the appropriate district court alleging the charge(s) on which the seizure is recommended. When appropriate, the court will order that the product be seized by the U.S. marshal in that district.

In the event a firm wishes to contest the seizure, it must file a claim to the seized product(s) and an answer to the charge(s) made by FDA. The case is heard by a judge, or a jury if requested by the claimant. After a verdict is reached, and a decision is handed down, the right of appeal to the court of appeals and, ultimately, the Supreme Court is available.

REGULATORY ACTIONS TAKEN  
ON FIRMS BY FDA

FDA has taken regulatory actions against each of the firms in our review. FDA has conducted inspections, issued regulatory letters, seized products, and sought injunctions against two of the firms--Naremco and Dan-Mar--for marketing products which FDA considered misbranded, adulterated, and/or food additives and new animal drugs for which no regulation for use had been issued. Both of these firms felt that gentian violet (the substance in question) was a generally recognized as safe substance; had been given prior sanction; and was, therefore, being legally marketed.

FDA conducted one inspection of the third firm, AHP, which marketed its product from February to April 1972. FDA told us that it has never brought criminal prosecution against any gentian violet manufacturer. This firm was advised by FDA in April 1972 that its product, an animal feed premix containing gentian violet, was a nonapproved feed additive for which no regulation for use had been issued. The firm then stopped marketing the product.

Naremco

Naremco was established during the 1950s as a subsidiary of Hoffman-Taff, Inc., Springfield, Missouri, and was called the National Remedy Products Company. In 1957, it became a separate entity called Naremco.

According to FDA officials, Naremco has manufactured and sold products which were considered misbranded or improperly labeled, adulterated, and food additives, and/or new animal drugs for which no regulation for use had been issued. An FDA inspector, in a report on a September 15 and 16, 1971, inspection, stated that the firm ignored citations, advisory letters, and warning letters and continued to manufacture and sell food additives and new animal drugs in violation of the act.

From 1955 to 1978, Naremco and/or its products were the subject of 12 inspections. Following these inspections, FDA claimed that Naremco had committed certain violations, including (1) misbranding or improper labeling, (2) illegal manufacturing and marketing of new animal drugs and/or food additives without prior approval from FDA, and (3) product adulteration. (App. I contains information on FDA inspections of Naremco and/or its products.)

The earlier products contained as many as 12 active ingredients, 1/ one of which was gentian violet. The acting director, Division of Drugs for Avian Species, BVM, told us that early concerns about these products were not directed specifically at the safety of gentian violet but rather at proper labeling of substances used in veterinary medicine and activities for food-producing animals because this was FDA's practice at that time. For instance, in a July 12, 1963, letter, FDA advised the firm that its Ferro-Lac Swine Formula and Ferro-Lac Calf and Cattle Formula Concentrate contained inadequate amounts of the ingredient sulfonamide for the recommended uses. Also, FDA stated that the labeling of the Ferro-Lac Swine Formula should not have suggested that the product, when fed to the sow, would prevent iron deficiency anemia in young pigs.

From 1960 to 1965, FDA inspections disclosed that the firm continued to market products similar to pre-1960 products but with changes in formulations and label claims. According to Naremco officials, the firm believed that its products were not new animal drugs or food additives subject to the act, because of the long history of the use of gentian violet and the April 13, 1961, letter from FDA's Commissioner. (See p. 10.)

During the period 1965 to 1971, FDA's inspections disclosed that Naremco's products had been reformulated--the number of active ingredients being reduced from 12 to 3 (gentian violet, sodium propionate, and sodium phthalylsulfacetamide).

In June 2, 1965, and January 26, 1966, letters, FDA advised the firm that it considered these products to be new animal drugs and/or food additives, since the products were intended for use on animals or in animal feed. Therefore, FDA maintained that such products would require a NADA and/or a FAP depending on the label directions for use.

In an October 15, 1969, letter, FDA informed Naremco that FDA had reviewed the firm's labels for the "Ferro-Lac Calf Boluses," "Ferro-Lac For Dogs," and "Ferro-Lac Cat Tablets."

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1/Ferric choline citrate, Menadione sodium bisulfite (source of vitamin K), Methylrosaniline (gentian violet), Sodium propionate, Zinc sulfate, Cupric sulfate, Cobalt sulfate, Magnesium sulfate, Potassium iodide, Potassium chloride, Manganese sulfate, and Citric acid.

FDA contended that these products failed to comply with the act and were misbranded or mislabeled because the firm had not demonstrated to FDA that they produced the effects intended.

Naremco officials disputed FDA's position claiming their products were generally recognized as safe, based on prior use in food and as a drug. Therefore, the firm stated that it saw no need to submit a NADA or a FAP. To do so would constitute an admission that their products were new animal drugs and/or food additives, which they felt was not the case.

From 1965 to 1975, FDA seized more than 15 Naremco products in various districts, which resulted in as many as 10 litigations--9 contested seizure actions and 1 injunctive action. The basis for seizure was that, in FDA's opinion, these products were unsafe under the act because they were misbranded, adulterated and/or food additives, or new animal drugs for which no regulation for use had been issued. (See app. II.)

During an April 21, 1961, inspection, FDA attempted to seize two of the firms' products--"Ferro-Lac Swine Formula Concentrate" and "TSC-80"--citing these products on charges of misbranding due to false and misleading claims. However, seizure of Ferro-Lac resulted in the product being destroyed in March 1963, because the firm failed to contest the seizure. FDA decided not to follow through on the seizure of the firm's TSC-80 product, because FDA felt that the product's labeling claims were not excessive enough to justify seizure.

After FDA seized some of the firm's other products containing gentian violet, Naremco contested the seizures. As a result, Naremco was involved in 10 court cases. (See app. III for details.) In all but one case, judgment was granted to FDA. When appealed, the decisions from the lower court were upheld by the higher courts. Some of these cases are discussed below.

The most recent case involving Naremco was a suit brought by FDA to stop Naremco from future interstate sale of gentian violet products used as animal drugs or additives in animal feed until premarketing approval was obtained from FDA. (See p. 7.) Judgment was granted to FDA in April 1977.

United States v. 41 Cases, More or Less of an Article of Food and Drug (Myconox), Civ. No. 4617 (E.D. Tex. 1966), and United States v. 7 Cases xxx and 12 Cases xxx of an Article of Food and Drug (Ferro-Lac), Civ. No. 4619 (E.D. Tex. 1966) was a consolidation of two cases with a jury trial in Tyler, Texas, involving both Myconox and Ferro-Lac.

The product Myconox was labeled as containing methylrosaniline chloride and sodium propionate for the treatment of avian mycosis. The Ferro-Lac Improved Poultry Formula Concentrate contained these additives as well as sodium phthalysulfacetamide for the prevention and treatment of non-specific enteric infections in poultry. FDA produced experts who testified that they were unaware of any general recognition of safety for either of these products for their labeled uses. The jury found that myconox was a new drug and a food additive with no clearance and was misbranded as charged. The jury found also that Ferro-Lac was a food additive not generally recognized as safe and effective for labeled claims. The court ordered both of the seized products to be condemned. The verdict was appealed, and the fifth circuit court upheld the verdict.

In United States v. An Article of Food and Drug xxx Naremco MediMatic Free Choice Poultry Formula (Medicated), Civ. No. 986 (W.D. Ark. 1966), judgment was granted to Naremco. FDA charged the product with being misbranded and adulterated. The court ruled that, since the product was not labeled as a food or labeled to be mixed with food, it could not be found to be adulterated as a food within the meaning of the act. The jury was therefore asked to disregard the food additive charge. The jury found the product not misbranded due to false claims. The seized product was returned to the firm.

FDA had considered appealing the ruling on this case, because it felt that the ruling did not appear to be consistent with the statutory definition of a food additive. However, FDA decided not to appeal because the same issues, involving similar products, were being argued in a case in Tyler, Texas.

#### Dan-Mar

Dan-Mar, another firm against which FDA sought formal regulatory actions, was incorporated in July 1972, at which time the firm began manufacturing and distributing the product, "Dye-Gen" (1.65 percent gentian violet), a premix animal

feed additive, without FDA approval. In addition to the basic Dye-Gen mold inhibitor product, the firm manufactured two other products containing gentian violet, "Dye-Gen Water Soluble and Dye-Gen Pink Eye and Blue Dressing Spray." The Dye-Gen Water Soluble also contained gentian violet as its only active ingredient and was intended for use in poultry drinking water to inhibit the growth of mold and fungi in animal water troughs and water lines. Dye-Gen Pink Eye contained both gentian violet and neomycin sulfate as active ingredients and was used for pink eye, cowpox sores, surface cuts, minor wounds, scratches, harness sores, and skin abrasions and to aid in the prevention and control of superficial infections for livestock. This product was voluntarily taken off the market by the firm in October 1977.

From 1973 to 1977, FDA conducted five inspections of Dan-Mar and/or its products. (See app. I.) FDA made the first inspection on June 28, 1973, as a result of an industry complaint that the firm was marketing a nonapproved animal feed additive containing gentian violet. The inspection disclosed that the firm was marketing and labeling gentian violet solely as a chemical rather than as an animal feed additive or as an animal drug. Dan-Mar maintained that gentian violet was generally recognized as safe because of its long history of use and that its products were in compliance with the act.

Additionally, the firm was notified by FDA that Dye-Gen was a new animal drug and food additive during an inspection made on June 5 and 6, 1974. However, according to the district office inspection report, Dan-Mar claimed that this product was sold as a chemical rather than feed additive or drug.

According to the FDA inspection report made on June 28, 1973, Dan-Mar claimed that marketing was only in Georgia; however, an FDA inspection of a feed mill in North Carolina disclosed that the firm's gentian violet product was on hand and was being used in turkey feed as a mold inhibitor. The inspection report also stated that the shipment of gentian violet to North Carolina had been made on June 4, 1973. The inspection report stated that the firm had apparently been promoting the product as a chemical under the trademark "Dye-Gen." Promotion was done by salesmen since no literature was available and no claims were made on the label. No regulation had been issued.

In a March 6, 1973, letter from Dan-Mar's consultant to BVM, the consultant had requested FDA's comments on the sale of the product, Dye-Gen, as a feed additive. In a May 2, 1973, letter, BVM responded as follows:

"Gentian violet for use in animal feeds would be a drug as defined by the Food, Drug, and Cosmetic Act since it is recognized in the United States Pharmacopoeia, [1/] and has no recognized nutritional or technical effect in such feeds. In fact, we are unaware of adequate published scientific data to support the use of gentian violet in the feed of animals for any purpose. Therefore, the intended use of the drug would cause it to constitute a 'new animal drug' which may not be commercially marketed in the absence of an approved new animal drug application. This is true whether or not the labeling bears any therapeutic indications."

Other inspections made by FDA in June 1974, July 1974, March 1975, and October 1977 disclosed that Dan-Mar was:

- Continuing to manufacture and distribute Dye-Gen without an approved new drug application.
- Distributing the product as a poultry feed additive.
- Refusing to allow FDA access to production and distribution records.

FDA seized Dan-Mar's products on a number of occasions before 1978 and cited the company on adulteration, feed additive, and new animal drug charges. Dan-Mar was involved in as many as five litigations with FDA--four seizure actions and one injunctive action. (See app. III.) Dan-Mar failed to contest these seizures and FDA was awarded a "Default Decree," and the products were destroyed by a U.S. marshal. There were also several other seizure actions instituted against the firm; however, they were disapproved or withdrawn because of pending litigation or, by the time the U.S. marshal arrived to seize the product, all goods had been sold.

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1/A publication listing drugs and medicines and describing their preparation, properties, uses, etc.



In recommending seizure of Dan-Mar products, FDA maintained that the products were (1) adulterated, (2) misbranded, and (3) food additives, which eventually resulted in an FDA injunctive action being brought against the firm.

Dan-Mar's most recent case, United States v. Dan-Mar Enterprises, Inc., et al. (see p. 9), was an action brought by FDA to enjoin Dan-Mar from future interstate sale of gentian violet products used as new animal drugs or animal food additives until premarketing approval was obtained from FDA.

This case involved the products, Dye-Gen Mold Inhibitor and Dye-Gen Pink Eye, both containing gentian violet as the active ingredient. The dispute involved whether Dye-Gen Mold Inhibitor was a food additive and whether Dye-Gen Pink Eye was a new animal drug. The focal issue with respect to both products was essentially the same--general recognition of safety.

The firm contended that both of its products were in fact "generally recognized as safe and effective" for their intended uses, basing this belief on gentian violet's long history of use in poultry. FDA maintained that Dan-Mar's products were not generally recognized as safe and, therefore, were food additives or new animal drugs, respectively, within the meaning of the act.

The court held that, since no food additive regulation or exemption authorizing the use of either gentian violet or Dye-Gen Mold Inhibitor had been issued pursuant to 21 U.S.C. 348 and since Dye-Gen Mold Inhibitor was a food additive, it was unsafe under 21 U.S.C. 348(a) and, therefore, was an adulterated food product. Similarly, the court said, if there was no approval of a NADA authorizing the use of Dye-Gen Pink Eye, and Dye-Gen Pink Eye was a new animal drug, then it was unsafe under 21 U.S.C. 360b(a)(1) and, therefore, was an adulterated drug product.

The introduction into interstate commerce of adulterated foods or drugs is prohibited by 21 U.S.C. 331(a), and the manufacturing, packing, and labeling of adulterated foods and drugs after shipment of one or more of their components in interstate commerce is prohibited by 21 U.S.C. 331(k), according to the court. Thus, 21 U.S.C. 332(a) gives the district courts jurisdiction to restrain violations of 21 U.S.C. 331.

The court's ruling on September 20, 1978, was that Dan-Mar's products were not generally recognized as safe and effective for their intended uses and, therefore, Dye-Gen Mold Inhibitor was a food additive, and Dye-Gen Pink Eye was a new animal drug. The court restrained the firm from conducting any further activities involving either product.

#### CONCLUSIONS

The firms involved in our review have attempted to market gentian violet, both alone and in combinations with other ingredients, alleging that their products were generally recognized as safe and, therefore, exempt from FDA regulations.

FDA seized a number of shipments of the firms' products over the years, claiming they were new drugs adulterated by virtue of the fact that their chemical combinations were not in conformity with an exemption or regulation promulgated pursuant to the FD&C Act (21 U.S.C. 348). As a result, FDA and the firms have been involved in a number of court cases. The courts have consistently supported FDA's actions by stating that, because of the absence of tests or investigations to determine efficacy or safety, these products have never been generally recognized as safe and effective for the uses intended.

Our review of records involving inspections, seizures, and court cases of the firms indicated that FDA's actions were not unreasonable.

## CHAPTER 5

### ALLEGATIONS OF HARASSMENT

Naremco has alleged that certain actions taken by FDA were unreasonable, overstepped agency authority, and/or were deliberate attempts by FDA to discredit or drive the firm out of business. Other firms believed that their problems with FDA stemmed from FDA's extensive involvement with Naremco. Naremco believed that FDA has followed a consistent pattern of harassment toward the firm for 25 years. Naremco officials alleged that FDA took a number of actions which resulted in Naremco's reputation being discredited. Naremco stated that FDA:

- Seized its products in four separate districts in 1966 and then refused to consolidate or negotiate settlements in these cases as requested by the firm.
- Misinformed various Members of Congress as to the firm's activities.
- Improperly advised various Naremco customers and State agencies that Naremco's products were being sold illegally.
- Improperly advised an official of the U.S. Department of Agriculture, Residue Evaluation and Planning Staff, Scientific Services, that the company's products could not be legally sold.
- Failed to notify other firms marketing gentian violet that a U.S. court of appeals ruled that the sale of gentian violet without an approved FAP or NADA was illegal.
- Interfered with Naremco's attempts to export a gentian violet food additive.
- Improperly took actions to prevent Naremco from marketing products at a poultry convention in 1975.

--Improperly published a 1974 court decision in the February 1978 "FDA Consumer." 1/

In our review, we found no evidence to support the above allegations. The acting director, Division of Drugs for Avian Species, BVM, acknowledged that certain statements made in correspondence sent to Members of Congress may have been inaccurate but indicated it was not FDA's intention to discredit Naremco or its products.

It appears that FDA's actions were not aimed at discrediting Naremco or its products but at providing Members of Congress with as much information as possible to indicate what had transpired between FDA and Naremco regarding gentian violet. Each of Naremco's allegations is discussed in more detail below.

CONSOLIDATION OF COURT CASES AND FDA'S  
REFUSAL TO NEGOTIATE A SETTLEMENT

In 1966, FDA seized five of Naremco's products in four districts, resulting in four separate court cases. The products were cited on charges of being adulterated in that they were (1) unapproved food additives, (2) new drugs without approved new drug applications, and/or (3) misbranded because, according to FDA, the products were not effective for the claims made.

On July 7, 1966, Naremco's attorney requested that these actions be consolidated in one jurisdiction because:

- All the cases were filed at about the same time.
- All products involved were manufactured by Naremco.
- Naremco filed claims and answers on behalf of each case.
- Naremco requested a jury trial as to all fact issues.

In a July 29, 1966, letter to the U.S. Attorney General, FDA's assistant general counsel set forth reasons for FDA's

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1/The "FDA Consumer" is an FDA publication listing judgments, decrees, court orders, and other subjects covered by the act.

refusal to consolidate the cases. The assistant general counsel stated:

"Under the provisions of 21 U.S.C. 334(b), consolidation of multiple proceedings is authorized when the same claimant and the same issues of adulteration or misbranding are pending in two or more districts. While the claimant, Naremco, Inc., is the same in all \* \* \* cases, none of the issues of misbranding and adulteration are the same. Each charge of adulteration alleges that the food additives are unsafe in that their use and intended use is not in conformity with 21 U.S.C. 348, and as each product has a different use and intended use (i.e., 'Myconox'--an aid in the control of mycosis and prevention of iron deficiency anemia in broilers and market turkeys; 'Naremco Medi-Matic' \* \* \* prevention of enteric infections in chickens and turkeys) and the adulterations are not the same. Similarly, the issues involved in the misbranding allegations, whether the product is adequate and effective in the control or treatment of specific diseases and conditions involving specific animals, are not the same. The statutory requirements for consolidation of these cases are, therefore, not satisfied."

Naremco officials told us that, on several occasions, the firm offered to negotiate a settlement with FDA which would allow them to continue marketing the products while they performed the tests required by FDA.

A meeting between the chief, Division of Case Guidance Branch, BVM, and a Naremco representative was held on May 29, 1968, to discuss the difficulties the firm was having with FDA. The BVM official advised the Naremco representative that there were three courses of action which the firm could take:

--Continue its present course of contesting the seizures.

--Enter into a consent decree in each case providing for relabeling of the seized products under FDA's supervision, so as to bring the seized products into compliance.

--Submit scientific data in support of a new drug application.

The firm, believing that its products were being legally marketed, contested the seizures. In an August 8, 1968, letter, the former Commissioner of Food and Drugs pointed out that FDA's Bureau of Regulatory Compliance told the firm in a July 25, 1968, letter that:

"The Act does not provide any basis upon which we can enter into interim arrangements which would postpone pending litigation, while at the same time allowing distribution of products considered in violation."

Both the former Commissioner in his August 8, 1968, letter, and the director, BVM, in a January 12, 1972, letter, told the firm that FDA would be pleased to discuss the issue of relabeling and/or reformulation of Naremco's seized products. However, this could only be accomplished if the firm filed an appropriate consent decree for condemnation of the seized products with the various court jurisdictions involved. Further, the decree would entail an agreement on Naremco's part that each product was adulterated and misbranded as charged, followed by provisions for relabeling under the supervision and concurrence of FDA.

According to a Naremco official, as a good faith effort on Naremco's part, the firm, in December 1971, offered to sell its products as chemicals without labeling claims. In a December 16, 1971, letter, FDA told Naremco that gentian violet had a valid chemical use and, therefore, could be marketed but only as a chemical for which purpose it would not be subject to the FD&C Act. FDA maintained that, if gentian violet was sold for use in animals or in animal food, its status would immediately change to that of a drug or a food additive depending upon the labeling claims.

A December 20, 1971, letter from Naremco in response to FDA's position stated:

"We cannot be permanently satisfied with label listing of gentian violet as a non-active ingredient but if we can by doing this get these products out of the courts, and open the door to submission of data which we can hope will lead to approval of medicated labeling acceptable to FDA, then you have our immediate and wholehearted cooperation."

Naremco cited this as an example of the firm's good faith efforts to deal with FDA.

INFORMATION PROVIDED TO MEMBERS OF CONGRESS ON NAREMCO'S ACTIVITIES

Naremco said that FDA misinformed Members of Congress of the firm's activities and the status of its products. Naremco cited a number of instances in which FDA, in responding to requests for information between 1967 and 1978, made statements which Naremco believed to be untrue and damaging to the firm's reputation. For example, FDA's Office of Legislative and Governmental Services stated in several letters written to Members of Congress in 1967:

"We had reviewed no safety data, either in the literature or in the form of direct submissions by the firm.

"Following the enactment of the 1962 Amendments, the firm was advised on various occasions that their products which had undergone several label and formula changes were now new drugs and food additives."

Naremco said that FDA did not notify them until June 2, 1965, that any of its products were considered to be new animal drugs.

According to a report of an FDA inspection in February 1963, an FDA inspector determined that one of Naremco's products containing gentian violet was possibly a new drug. The inspection report indicated that this finding had been discussed with a Naremco official, who stated that the product was not a new drug.

Naremco also told us that, in several letters sent to Members of Congress, FDA made the following statements which were damaging to the firm's reputation.

- "No \* \* \* applications have ever been approved for any of the Naremco drug products, although many if not all of their animal drugs, are new animal drugs within the statutory definition."
- "No food additive petition has ever been received by FDA for any Naremco food additives. As with their drugs, most if not all of their food additives fall within the statutory definition."
- "Neither FDA nor experts in the field are now or ever have been made aware of any scientific data attesting to the safety and efficacy of Naremco's drugs or the safety of their food additives."
- "Despite these court decisions, the firm has continued to market its products without any attempt to comply with the statutory requirements of preclearance. They had been repeatedly told by FDA, before, during, and after the earlier litigation against their products, that these products could only be properly marketed through preclearance and not through mere label changes."

In reference to these statements, Naremco told us that it submitted a NADA to FDA on June 16, 1965, to add an additional claim for one of its products. We verified that Naremco did submit the NADA. FDA rejected the application on grounds that it was incomplete, and Naremco withdrew it. FDA records show that the firm then continued to market that product and others with similar claims without FDA approval.

Naremco said that it had submitted a 12-week study to FDA in 1959 in support of the efficacy of one of its products. In a September 4, 1959, letter, FDA made the following comments regarding the study:

- "We do not think the results of studies and other data set forth herein provide impressive and conclusive evidence of the value of the Ferro-Lac products."



--"Much of the material in the submitted folder is in the nature of testimonials which are generally of little or no significance to the evaluation of a product."

--"The reports of various tests or studies generally do not show a significant difference in the results between the Ferro-Lac groups and control groups."

--"We question, therefore, that the material you have submitted substantiates the claims proposed for the Ferro-Lac products."

In a June 30, 1978, letter to a Member of Congress, FDA had incorrectly stated that this study was a 15-day study. The firm cited this as an intentional error on FDA's part to discredit its reputation and products.

Naremco stated that during the period FDA was sending out correspondence to Members of Congress regarding the illegality of its products, the firm had other products on the market which did not contain gentian violet and were being legally sold. Naremco contended that for FDA to say "most if not all" of the firm's products were new animal drugs or food additives discredited the firm's reputation and placed all of the firm's products under suspicion, causing Naremco to lose some of its customers.

The acting director, Division of Drugs for Avian Species, BVM, acknowledged that the statements may have been inaccurate but indicated it was not FDA's intention to discredit Naremco or its products in any way. He stated such errors were unintentional.

We identified inaccuracies in correspondence FDA sent to Members of Congress. However, we found no evidence to indicate these inaccuracies were deliberate actions to discredit Naremco's reputation or its products.

ADVICE PROVIDED TO VARIOUS NAREMCO  
CUSTOMERS AND STATE AGENCIES CONCERNING  
THE LEGALITY OF NAREMCO PRODUCTS

Naremco told us that FDA went out of its way to inform Naremco customers and State agencies that some Naremco products had not been approved by FDA and were, therefore, being sold illegally. Naremco pointed out that FDA informed poultry

users and State agencies in several letters written between 1967 and 1978 that gentian violet was neither generally recognized by experts as being safe for use as an animal feed additive nor was it a prior sanctioned substance. FDA stated in these letters that it had approved no NADAs for any brand of gentian violet and that it was illegal under the act to market new animal drugs without approval.

Naremco told us that, when customers were advised that FDA considered the firm to be illegally marketing products, no company wanted to do business with them.

The acting director, Division of Compliance, BVM, said that it is FDA's policy to give its position when asked about the status of any product. Also, in a September 8, 1975, letter to Naremco's attorney from FDA's Division of Federal-State Relations, the executive director of regional operations stated that:

"Acknowledgement of FDA's right to its expert opinion of the status of drugs and food additives is not only appropriate, but necessary to inform other regulatory agencies of these opinions. The policy of the Food and Drug Administration is to respond to requests for interpretation, opinion, and advice from state and local officials on matters of mutual concern and responsibility."

As indicated earlier, FDA did advise various Naremco customers and State agencies on several occasions of the status of gentian violet in response to their requests. In our opinion, FDA acted within its authority and regulations in responding to both Naremco customers and State agencies.

ADVICE PROVIDED TO A USDA  
OFFICIAL ON WHETHER NAREMCO  
PRODUCTS COULD BE LEGALLY SOLD

According to Naremco, FDA improperly advised an official of USDA's Residue Evaluation and Planning Staff that it was illegal to use gentian violet in poultry feed. This incident allegedly occurred in September 1975 after a Federal district court's ruling that certain of the firm's gentian violet products were generally recognized as safe and could be used as animal feed additives.

On September 16, 1975, a USDA official, addressing a meeting of poultry industry officials, was asked about the status of gentian violet. The official told us that he had been unaware of the legal status of gentian violet and, therefore, contacted FDA for additional information. The USDA official had later informed the participants of the meeting that, according to FDA, gentian violet had not been approved for mold control in poultry feed.

A Naremco representative at the meeting cited the recent court decision which held that certain Naremco products could be sold. The USDA official said that he was not aware of the court's decision and was merely passing on information obtained from FDA. Naremco officials believe that this is evidence that FDA, by misinforming the USDA official, wanted to disrupt the firm's business.

The USDA official told us that he could not recall the name of the FDA official he spoke with on September 16, 1975. However, he believed that the official probably told him that it was FDA's opinion that gentian violet was an unapproved food additive and animal drug.

The USDA official gave us a copy of a memorandum of another conversation with an FDA official and a member of the USDA official's staff. The conversation took place on September 17, 1975. According to this memorandum, the FDA official informed the USDA staff member of the 1975 court ruling that gentian violet was to be considered generally recognized as safe in animal feeds. 1/

NOTIFICATION TO OTHER FIRMS  
MARKETING GENTIAN VIOLET PRODUCTS  
OF THE COURT OF APPEALS' RULING

Naremco stated that FDA failed to notify other firms marketing gentian violet that a June 20, 1977, final order of a U.S. court of appeals 1/ held that the sale of gentian violet was illegal without an approved FAP or NADA.

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1/FDA later successfully appealed this ruling.

2/United States v. Naremco, Inc., a corporation and Waitman Patrick Scott and Dennis E. Jackson, Appellees, No. 76-1623

In an attempt to determine whether FDA was acting consistently towards other firms marketing gentian violet products, Naremco's attorney submitted a request to FDA asking for copies of all correspondence and memorandums of any meetings held between FDA and three other firms known to market gentian violet. The purpose of this request was to determine if FDA had notified other firms that the court found that the products containing gentian violet could not be marketed without prior FDA approval.

An October 19, 1977, letter to Naremco's attorney from the chief, Case Guidance Branch, Division of Compliance, BVM, stated that FDA files showed a June 21, 1977, letter of notification had been sent to one firm marketing gentian violet products. (This firm was not included in our review.) However, the director, Division of Compliance, BVM, told us that FDA had taken prompt action to notify all firms known to be marketing gentian violet for veterinary purposes. The director provided us with letters sent to eight additional firms on June 21, 1977. However, one firm, Dan-Mar was not sent a letter until November 1, 1977. The director was unable to explain why FDA had delayed notifying Dan-Mar until such time.

It appears that FDA promptly notified all but one firm known to be marketing gentian violet for veterinary purposes of the court's decision. We were unable to determine why FDA delayed notifying the one firm, Dan-Mar, for 4 months.

INTERFERENCE WITH NAREMCO'S ATTEMPTS  
TO EXPORT A GENTIAN VIOLET FOOD ADDITIVE

Naremco claimed that FDA interfered with the firm's attempt to export gentian violet products. In June 1977, Naremco began to explore the possibility of selling gentian violet as a mold inhibitor in animal feeds to foreign countries. The FD&C Act permits export of unapproved food additives if they meet specific criteria. The food additive must:

- Conform to the specifications of the foreign purchaser.
- Not be in conflict with the laws of the country to which it is intended to be exported.
- Be labeled intended for export on the outside of the shipping package.

--Not be sold or offered for sale in domestic commerce.

Naremco officials said that, in June 1977, the firm requested the assistance of USDA's Foreign Agricultural Service in determining whether a number of foreign countries would allow the import of gentian violet. The USDA official responsible for assisting Naremco told us that he contacted the USDA liaison official in the U.S. embassies in these countries to ascertain the countries' positions on the import of gentian violet.

The official said that replies from these countries fell into three categories: (1) the product was either already being imported or could be imported to the country, (2) since the product was banned for use as a feed additive in the United States, it would also be banned in the foreign country, and (3) additional information was requested. These replies were relayed to Naremco as they were received.

In August 1977, one country requested specific information on FDA's position on the use of gentian violet as a mold inhibitor in livestock feed. The USDA official said that he contacted FDA on August 23, 1977, requesting this information. On September 1, 1977, the acting director, Division of Compliance, BVM, responded to this request by stating that, in FDA's opinion, gentian violet was a suspect carcinogen for which more data was needed to determine its safety. The acting director further outlined the policy regarding exportation of a product to a foreign country. The acting director concluded by saying that, if the foreign government deemed the product acceptable for sale in its country, exportation could be permitted. According to Naremco, a number of countries declined permission for the sale of gentian violet because of FDA's September 1, 1977, letter.

Naremco officials believe that FDA went out of its way to notify foreign countries of the status of gentian violet in an attempt to disrupt Naremco's business. However, the USDA official told us that the September 1, 1977, letter was in response to USDA's request and that he could recall no further contact with FDA on the matter.

We found no evidence that FDA initiated contact with foreign countries about the status of gentian violet. However, we did note that, when foreign countries requested information on gentian violet, FDA gave its position. We believe that such an act on FDA's part was in line with FDA authority and responsibility.

ACTIONS TAKEN TO PRECLUDE NAREMCO  
FROM MARKETING PRODUCTS AT A  
POULTRY CONVENTION IN 1975

Naremco said that FDA overstepped its authority by taking actions to preclude the firm from marketing products containing gentian violet at a poultry convention in January 1975. Naremco officials told us that the firm was a victim of an incident which occurred at a Southeastern Poultry and Egg Association Convention in Atlanta, Georgia, in January 1975. According to the firm, an official in FDA's Atlanta district office contacted the executive secretary of the convention and requested that the executive secretary close down the firm's booth and confiscate its materials. The firm said that the executive secretary was able to persuade the FDA official that such action was not appropriate, and the matter was dropped.

We were unable to identify any evidence in FDA files that the alleged incident took place. The director, Division of Compliance, informed us that the FDA official who supposedly attempted to take such action was no longer with the agency. According to the acting director, Division of Drugs for Avian Species, BVM, and the director, Division of Compliance, BVM, any such actions on the part of an FDA official would have been inappropriate and without FDA authorization.

PUBLICATION OF A 1974 FEDERAL  
COURT DECISION IN THE  
FEBRUARY 1978 "FDA CONSUMER"

Naremco stated that FDA's publication of a 1974 court decision 1/ in a February 1978 issue of the "FDA Consumer" was an unreasonable action and an attempt to discredit the firm's reputation.

According to a Naremco official, FDA waited until 1978 to publish a 1974 court decision which cited Naremco's products on charges of being adulterated, misbranded, unapproved food additives, and/or new animal drugs for which no approval of a NADA had been issued. This official stated that he felt FDA's action was an attempt to discredit the firm and disrupt its business.

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1/United States v. Articles of Food and Drug Coli-Trol  
80 Medicated, Civ. A. No. 1413 (N.D. Ga. 1974).

An FDA attorney involved in FDA's regulation of gentian violet said that it was normal practice for the notice of judgment in a particular case not to be published in the "FDA Consumer" until the responsible attorney closes his files. These files may remain open for a number of years in the event similar matters are being considered. According to this attorney, the delay in the publication of the court's decision followed regular agency practice in these situations. We found no evidence that FDA's publication of the 1974 court's decision in 1978 was an attempt to discredit Naremc0 or disrupt its business.

NO EVIDENCE THAT FDA'S ACTIONS AGAINST  
DAN-MAR AND AHP WERE UNREASONABLE

A Dan-Mar official stated that he felt that FDA's refusal to allow his firm to market gentian violet products was due primarily to problems FDA had with Naremc0. FDA had taken a position that it would not allow Naremc0 to market gentian violet. This official stated that he believed, to appear consistent, FDA could not allow other firms to market gentian violet.

In our review, we found no evidence that FDA took unreasonable actions against Dan-Mar or other firms in order to appear consistent with actions taken against Naremc0. We believe that actions taken by FDA against Dan-Mar and other firms had no bearing on the history of litigation with Naremc0, and were consistent with FDA's assessment of the status of gentian violet.

AHP officials told us that they felt that they had followed FDA's instructions in that they had submitted safety and efficacy data and refrained from marketing gentian violet products after FDA had informed the firm that it was illegal to do so. In reference to the safety data, the firm also stated that it tried to comply with FDA requirements by conducting the necessary tests; however, it was frustrated by changing requirements regarding the safety of gentian violet. The AHP officials also stated that they believed that FDA's failure to approve gentian violet products resulted from FDA's intent to prohibit Naremc0 from selling such products.

AHP was the only firm in our review which voluntarily discontinued marketing its gentian violet product. In trying to comply with FDA safety requirements, however, changing

circumstances (see ch. 3) may have made it appear that FDA's requirements were unreasonable. FDA officials recognized that AHP had made an effort to complete the necessary testing and had refrained from marketing its gentian violet product; however, FDA could not ignore changing safety requirements in view of its responsibility to protect the public health.



## CHAPTER 6

### AGENCY AND INDUSTRY COMMENTS

The Department of Health and Human Services said that in general it agreed with the contents and conclusions of this report.

AHP, through its attorney, stated that this report contained a fair and accurate representation of the information the firm provided to us.

The other two firms in our review--Dan-Mar and Naremco--declined to comment on the report.

NarencoRESULTS OF FDA INSPECTIONS OF FIRMS IN GAO'S REVIEW

<u>Date</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
5/12/55	St. Louis	Ferro-Lac Powder	Made as part of the surveillance of a new firm located in Springfield, Missouri. The inspection was made to obtain a sample of one of their products for possible misbranding. Since St. Louis District had no file on this firm, an inspection was made in order to obtain current information.	The firm was offering a product for the treatment of a number of disease conditions. The firm was not giving adequate directions for use in these conditions, therefore, the product was misbranded. The product may also be subject to the new drug section of the Food and Drug Act and was being marketed without an approved new drug application.
3/19/56	St. Louis	Ferro-Lac Powder and liquid	Follow up to a citation letter. Inspection was also made to determine the present labeling used by this firm in the preparation of the veterinary product. Also, to determine the firm's present method of operations concerning this product.	The firm was still manufacturing and distributing the product Ferro-Lac which was still considered to be misbranded.

Naremo

<u>Date</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
4/21/61	St. Louis	Ferro-Lac and TSC-80 products, vitamins for animal use, veterinary drugs	To determine whether the firm had made label changes to comply with the FD&C Act. To determine sanitary conditions and controls employed by the firm in the manufacturing of veterinary drugs. Also, to determine whether the firm is using food additives or color additives in the manufacturing of veterinary drugs.	There were no unsanitary conditions noted during this inspection. The firm's Ferro-Lac and TSC products were misbranded due to broad and extravagant claims. However, the firm had been in correspondence with FDA and had been advised of the false and misleading claims. A memorandum dated March 15, 1961, advised the firm about Ferro-Lac. Another memorandum dated April 10, 1961, pointed out the discrepancies concerning TSC-32, TSC-80, and TSC-Soluble. This inspection revealed the firm was still shipping these products under the same violative labels. The firm apparently had not taken any steps to change these labels.
2/18 and 19/63	St. Louis	Calf Formula Soluble Small Animal Formula (Canine), Vita-Pak Soluble, Vitamin-Mineral preps for addition to feeds, remedies for digestive system and mastitis treatment.	To determine current labeling and manufacturing controls. Also to follow up on TSC-80 and Swine formula products.	Firm was manufacturing approximately 12 products, whereas in the past all manufacturing was done by Hoffman-Taft, Inc. Controls were questionable in that only one person weighed ingredients and few, if any, finished products were assayed. Several products appeared to be misbranded. The product Visco-Giene was cited for possible new drug charges.

Narenco

<u>Date</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
10/6 and 7/65	St. Louis	Visco-Giene Medi-Matic Vitamin mineral preps, for addition to feeds Veterinary products.	Followup to inspection dated February 18-19, 1963, and January 4, 1964, which disclosed control weaknesses and label discrepancies.	Inspection revealed inadequate manufacturing controls in that neither raw materials nor finished products were assayed, some raw materials were improperly identified in storage, and the firm's methods of storing labels could result in mix-ups. Visco- Giene was still being distributed without an effective new drug application and labeling for Medi-Matic had not been corrected. Several of the firm's products contained verxite, a regulated food additive and did not bear label statements conforming to 121.222 of the act.
12/5 and 6/67	Kansas City	Myconox and Poultry Formula Concentrate Vitamin-Mineral preps for animal feeds Veterinary drugs.	To bring files on the firm up to date.	The inspection showed only one basic change in labeling though the firm had discontinued Visco- Giene 30. Ferro-Lac Calf Formula Soluble, and Medi-Matic Block. Finished products were not assayed prior to distribution and manu- facturing controls were weak. The only new product was an iron preparation for treating anemia in dogs and horses.

Narempco

<u>Date</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
9/15 and 16/71	Kansas City	Mycotrol-P, Mycotrol-S, Entrol-P, Entrol-S, Entrol-C, Coli-Trol 80 Myconox and Medi-Matic vitamin-mineral preparation for animal feed. Veterinary drugs and feed premixes	To determine the status of products involved in previous litigation and to determine current operations.	The firm continued to manufacture the same general line of veterinary drugs and feed premixes only under different product names, and at different concentrations, but generally containing the same mis- branding claims for active ingre- dients methylrosaniline chloride, sodium phthalysulfacetamide - hexamethylpararosaniline chloride, and/or sodium propionate. The firm had ignored citations, advisory letters, and warning letters. Seizures were contested, and even though courts found the firm's products to be new animal drugs without approved NADAs and the products to contain unsafe food additives, the firm merely revised formulas, changed the product names, and continued marketing similar veterinary drugs and premixes in violation of the act.
4/15 and 19/74	Kansas City	Entrol-P Entrol-S Mycotrol-P gentian violet raw materials	In response to a BVM memorandum dated March 27, 1974, requesting investigation of firm's current operation in support of reactivating an injunction request previously submitted to BVM.	Revealed operations essentially unchanged, with virtually the same products manufactured now as in 1971. These products contained Methylrosaniline chloride (gentian violet), Phthalysulfacetamide, Sodium pthalysulfacetamide. Since the pre- vious inspection, the firm had added only one other product to the line, called GV-11. Inspection also revealed manufacturing procedures essentially unchanged.

<u>Narencoc</u>	<u>Date</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
	4/15 and 19/74 (continued)				
	8/26/74	Kansas City	GV-11	Followup to April 15-19, 1974, inspection to determine whether firm was in compliance with FDA regulations.	A brief review of controls revealed that the firm does no assay of either raw materials or finished products, with no record maintained of incoming supplier lot numbers, and batch records being incomplete in that no listing was made of product blended into a new batch.  Inspection revealed firm's operations unchanged. Firm continued to manufacture animal's feeds containing gentian violet without approval of a food additive petition or new animal drug application. Firm also continued to manufacture and distribute the product GV-11 for which no claims were made.
	9/27 and 28/76	Kansas City	GV-11 and five vitamin/mineral premixes	Followup to memorandum dated April 29, 1976, to determine firm's compliance with court order involving "Good Manufacturing Practices."	Found firm complying with terms of court order and producing only GV-11 and five vitamin/mineral premixes.
	8/3/77	Kansas City	GV-11 and 5 percent GV	Inspection conducted at request of Kansas City Compliance Branch to determine the firm's compliance with the provisions of injunction.	Found firm had discontinued domestic sales of products containing gentian violet, but continued to manufacture GV-11 and 5 percent gentian violet for export.
	5/3/78	Kansas City	All products containing gentian violet.	Conducted under injunction No. 75CV147-S which prohibits the sale of products containing gentian violet, with exception of export sales.	Found firm continuing to manufacture a small amount of product for export.

Dan-Mar Enterprises

<u>Date</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
6/28/73	Atlanta	Dye-Gen (1.65 percent GV) Mold Inhibitor	Followup on an industry complaint that Dan-Mar was marketing a nonapproved animal feed additive, gentian violet.	Dan-Mar was labeling and promoting its product as a chemical under the trademark "Dye-Gen" rather than as an animal feed additive or as an animal feed drug. At one location a lot of gentian violet was being used in turkeys' feed as a mold inhibitor.
6/5 and 6/74	Atlanta	Dye-Gen (1.65 percent GV) Dye-Gen Soluble Concentrate	This inspection was a followup to reports that the firm was distributing poultry feed with gentian violet as an active ingredient.	Inspection was terminated because management refused access to production and distribution records. No samples or distribution information was obtained.
7/10/74	Atlanta	Dye-Gen (Gentian Violet)	Followup to a June 6, 1974, inspection, which was limited to a sample and distributed literature on the product for regulatory consideration.	Firm manufactured and distributed Dye-Gen as a poultry feed additive without approved new drug application (claimed to have submitted a protocol to FDA).
3/11/75	Atlanta	Dye-Gen (Gentian Violet)	To obtain a sample and distributed literature on the product in response to a memorandum dated February 3, 1975, from the Compliance Branch for regulatory consideration.	Use of gentian violet in poultry and animal feeds without approval from FDA. (Calcozine methyl violet now in liquid form.)
10/19 and 20/77	Atlanta	Dye-Gen Pink Eye Dye-Gen Mold Inhibitor	Followup on reports that Dan-Mar was continuing to manufacture and market the two stated products illegally.	Feed additive and new animal drug charges—manufacturing and distributing Dye-Gen without approval from FDA.

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<u>AHP</u>	<u>District</u>	<u>Product</u>	<u>Purpose</u>	<u>Findings</u>
<u>Date</u> 6/5/73	Atlanta	ViGen	Initial inspection of the firm which was limited to documenting the return of a lot of ViGen which had been held for sale at Animal Services, Inc., Forest, Mississippi, but which had been shipped without being labeled "For experimental use only." Additionally, a sample of a recent batch of ViGen was collected. This inspection was prompted by the inspection of Animal Services, Inc., on March 13, 1973.	The firm manufactured only one product, ViGen, an animal feed premix containing gentian violet as an active ingredient. Gentian violet is a nonapproved feed additive and a Veterinary Investigational New Animal Drug is on file for this premix. Distribution was limited to three researchers.



FDA SEIZURES OF CERTAIN VIOLET PRODUCTS MARKETED BY FIRMS IN GAO'S REVIEW

<u>NarencO</u>	<u>Date</u>	<u>Location</u>	<u>Product(s)</u>	<u>Charge(s)</u>
	1/23/63	Holmes Serum Supply Company, Inc. 225 East Washington Springfield, Ill.	Ferro-Lac swine formula concentrate	Misbranded
	5/10/66	Corn Belt Hatcheries Hope, Ark.	Medi-Matic free choice poultry formula	Adulterated, misbranded
	5/24/66	Henry County Service Center, Inc. Atkinson, Ill.	Ferro-Lac swine formula concentrate	Adulterated, misbranded
	5/26/66	East Texas Poultry Supply P. O. Box 994 Center, Tex.	Ferro-Lac Mycnox	Misbranded, unapproved food additive unapproved new drug
	5/31/66	East Texas Poultry Supply 730 E. Shelbyville Street Center, Tex.	Ferro-Lac poultry formula concentrate	Unapproved food additive, misbranded
	7/16/68	Animal Health Sales, Inc. Main Street Selbyville, Del.	Mycnox medicated	Unapproved new drug, adulterated, unapproved food additive, misbranded
	9/29/71	Hannah Supply Company Gainesville, Ga.	Coli-Trol 80 medicated, Myconox-LF, F4C-60, Mycotrol-P, Entrol-P, Entrol-S	Adulterated, misbranded, unapproved new animal drug, unapproved food additive
	11/1/71	NarencO, Inc. 1724 Mt. Vernon St. Springfield, Mo.	Medi-Matic free choice poultry formula Mycnox medicated	Adulterated, misbranded, unapproved new animal drug
	1/12/72	Wilbur-Ellis Company P. O. Box 12 Heber, Calif.	Entrol-C medicated	Adulterated, unapproved new animal drug, misbranded
	11/1/72	Wilbur-Ellis Company Clovis, N. Mex.	Ferro-Lac calf boluses Ferro-Lac calf formula	Adulterated, unapproved new animal drug, misbranded

Dan-Mar Enterprises

<u>Date</u>	<u>Location</u>	<u>Product(s)</u>	<u>Charge(s)</u>
4/21/75	Dan-Mar Enterprises, Inc. Commerce, Ga.	Cyanamid calcozine methyl violet Dye-Gen	Unapproved food additive, adulterated
2/21/76	Helena Animal Health 301 1st Avenue, N.E. Cullman, Ala. 35055	Dye-Gen soluble concentrate	Adulterated, unapproved food additive
6/7/76	Helena Chemical Company Highway 68 West Springdale, Ark.	Dye-Gen soluble concentrate	Adulterated, unapproved food additive, unapproved new animal drug
a/	Durham, N.C.	Dye-Gen	Adulterated

a/We were unable to find appropriate correspondence relating to this seizure. However, an FDA attorney provided us with the above information.

<u>AHP</u>	<u>Date</u>	<u>Location</u>	<u>Product(s)</u>	<u>Charge(s)</u>
	4/73 a/	Animal Services, Inc. 1052 West Third, Forest, Miss.	Vigen	Adulterated, unapproved food additive

a/FDA attempted to seize this product; however, the product was returned to the shipper (AHP) before the seizure action was carried out.

COURT CASES INVOLVING GENTIAN VIOLET PRODUCTS MARKETED BY FIRMS IN GAO'S REVIEWNaremo

<u>State case</u>	<u>Product</u>	<u>Filed</u>	<u>Charge</u>	<u>Decision</u>		<u>Appeal filed</u>	<u>Decision</u>	
				<u>Date</u>	<u>For</u>		<u>Date</u>	<u>For</u>
Texarkana, Ark.	Medi-Matic free choice Poultry formula	a/	Adulterated misbranded	11/66	Naremo	-	-	-
Tyler, Tex.	Mycnox Ferro-Lac (improved Poultry formula)	b/	Adulterated misbranded new drug	2/67	FDA	b/	1/70	FDA
Omaha, Neb.	Ferro-Lac calf and cattle formula (con- centrate) medicated	5/66	Adulterated misbranded new drug	9/70	FDA	-	-	-

a/We were unable to determine the date this case was filed. Naremo filed a claim and answer for the seized products May 16, 1966.

b/The products were seized on May 26 and 31, 1966. However, we were unable to determine the dates on which the complaints and/or appeal notices were filed.

Narengo

<u>State case</u>	<u>Product</u>	<u>Filed</u>	<u>Charge</u>	<u>Decision</u>		<u>Appeal filed</u>	<u>Decision</u>	
				<u>Date</u>	<u>For</u>		<u>Date</u>	<u>For</u>
Atkinson, Ill.	Ferro-Lac swine formula	5/66	New drug adulterated misbranded	12/68	FDA	2/69	4/70	FDA
Wilmington, Del.	Myconox medicated	7/68	New drug adulterated misbranded	9/71	FDA	-	-	-
Gainesville, Ga.	Myconox-LF Coli-Trol 80 F4C-60 Mycotrol-P Entrol-S Entrol-P	9/71	Adulterated new animal drug misbranded	2/74	FDA	9/74	9/75	FDA
Kansas City, Mo.	Medimatic Myconox medicated	10/71	Adulterated misbranded	1/74	FDA	-	-	-
San Diego, Calif.	Entrol-C medicated	1/72	New animal drug misbranded	6/73	FDA	a/	4/75	FDA
Jackson, Miss. <u>b/</u>	Myconox-LF Myconox-P GV-Eleven	5/73	Food additive new animal drug adulterated	-	-	-	-	-
Kansas City, Mo.	All products <u>c/</u> containing gentian violet	4/75	New animal drug	4/76	<u>c/</u>	2/77	4/77	FDA

a/We were unable to determine the date of the appeal.

b/This case was dropped because all of the products were under seizure in contested litigation.

c/Judgment was granted to FDA for all products cited except GV-11 medicated and GV-11 mold inhibitor based on the court's finding that the GV-11 products, when used according to the directions contained in the court-approved labeling, was neither a new drug nor a food additive. The other products included: Entrol-C, Entrol-P, Entrol-S, and Mycotrol-P, Mycotrol-S, Myconox-P, Myconox soluble, medi-Matic medicated, Ferro-Lac calf boluses, Ferro-Lac calf formula, and Myconox-LF. FDA appealed insofar as the GV-11 products, and the 8th Circuit court of appeals reversed the lower courts decision. Judgment was granted to FDA.

<u>State case</u>	<u>Product</u>	<u>Filed</u>	<u>Charge</u>	<u>Decision</u>		<u>Appeal filed</u>	<u>Decision</u>	
				<u>Date</u>	<u>For</u>		<u>Date</u>	<u>For</u>
Atlanta, Ga.	Cyanamid calcozine methyl Violet PPM liquid Dye-Gen (1.65 percent GV)	4/75	Adulterated	5/75	a/	-	-	-
Cullman, Ala.	Dye-Gen soluble concentrate	2/76	Adulterated	4/76	b/	-	-	-
Fayetteville, Ark.	Dye-Gen soluble concentrate (Gentian Violet)	c/	Adulterated	9/76	d/	-	-	-
Gainesville, Ga.	Dye-Gen pink eye Dye-Gen mold inhibitor	1/78	New animal drugs food additives	9/78	FDA	11/78	1/79 e/	-
Durham, N.C.	Dye-Gen	5/78	Adulterated	2/79	f/	-	-	-

a/Case dismissed because the articles were no longer within the jurisdiction of the court at the time the U.S. marshal arrived to seize the articles. The seizure was not made and, therefore, the complaint of forfeiture filed on April 7, 1975, was dismissed on May 16, 1975.

b/Default Judgment and Order of Forfeiture entered May 1976. U.S. marshal destroyed property on June 27, 1976. Dan-Mar did not contest seizure.

c/We were unable to determine the date FDA filed this complaint.

d/Default Decree of Forfeiture entered October 1976. The U.S. marshal destroyed the property on Jan. 9, 1976. In a Default Decree of Forfeiture, the claimant, Dan-Mar, did not contest seizure.

e/Dan-Mar appealed the district court's decision. However, on January 22, 1979, Dan-Mar requested a voluntary dismissal. FDA agreed to the dismissal.

f/Default Decree entered February 1979. Seized articles were destroyed. Dan-Mar did not appear in court to contest seizure.

<u>AHP</u>	<u>State case</u>	<u>Product</u>	<u>Filed</u>	<u>Charge</u>	<u>Decision</u>		<u>Appeal filed</u>	<u>Decision</u>	
					<u>Date</u>	<u>For</u>		<u>Date</u>	<u>For</u>
	Jackson, Miss.	ViGen	5/73	Adulterated food additive	a/	-	-	-	-

a/ FDA attempted to seize this product; however, the product was returned to the shipper (A.H.P.) before the seizure action was carried out. FDA filed a complaint of forfeiture on May 7, 1973.

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
OFFICE OF THE SECRETARY  
WASHINGTON, D.C. 20201

Office of Inspector General

JUN 18 1980

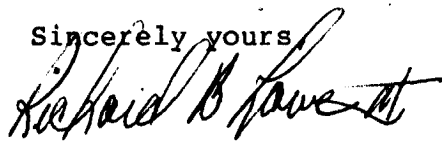
Mr. Gregory J. Ahart  
Director, Human Resources  
Division  
United States General  
Accounting Office  
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Gentian Violet: A Case Study of the Regulation of an Unapproved Food Additive/New Animal Drug." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,



Richard B. Lowe III  
Acting Inspector General

Enclosure



COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES ON THE  
GENERAL ACCOUNTING OFFICE'S DRAFT REPORT ENTITLED: "GENTIAN  
VIOLET: A CASE STUDY OF THE REGULATION OF AN UNAPPROVED  
FOOD ADDITIVE/NEW ANIMAL DRUG"

In general, the Department of Health and Human Services agrees with the content and conclusions of the report. GAO found no evidence that FDA's regulatory machinery was improperly used to force certain companies off the market or that FDA was unresponsive to efforts made in good faith by the companies to resolve problems with their applications.

Therefore, we have no comments regarding the substance of the report but rather offer the attached textual corrections to further contribute to the report's overall precision and accuracy.

GAO Note: Corrections to the text of the report were considered and made where appropriate.

*Fryer, Bouton and Warhall*  
*Attorneys*

*Robert H. Fryer*  
*Edmund J. Bouton*  
*Lawrence F. Warhall*  
  
*James J. Fleming*

*RFD No. 4*  
*33 Nashua Road (Route 102)*  
*Londonderry, New Hampshire 03053*  
*Telephone (603) 432-9566*  
*Cable: "Warlaw"*

June 18, 1980

Mr. Gregory J. Ahart, Director  
 Human Resources Division  
 U.S.G.A.O.  
 441 G. Street N. West  
 Washington, D.C. 20548

Re: Gentian Violet

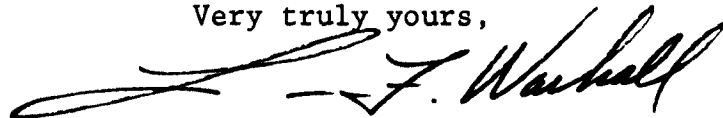
Dear Mr. Ahart:

Mr. Jack L. Radlo has asked that I as counsel for A.H.P. Inc., respond to your letter dated May 20, 1980 in regard to A.H.P. Inc.'s review and comments of the GAO's case study regarding Gentian Violet.

A.H.P. Inc.'s response is that the report is a fair and accurate representation of the information given to your office by it and also a fair and accurate representation of our discussions with your office's representatives with the exception of the comment on page six of the report...and A.H.P. Inc., are no longer in existence.." A.H.P. Inc. is indeed still in existence and is a viable corporation. Also obvious by its absence from your report is any mention of FDA's acceptance and approval of our efficacy data regarding the effectiveness of the claims of our N.A.D.A.

A.H.P. Inc. also notes that no proprietary information regarding its NADA has been disclosed.

Very truly yours,



Lawrence F. Warhall

LFW/jmw

cc: Mr. Jack L. Radlo

(108830)



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