to review by the Secretary to determine the allowability of costs.

(b) Costs incurred prior to the effective date of the project agreement are allowable only when specifically provided for in project agreement.

(c) Projects or facilities designed to include purposes other than those eligible under the pertinent Act shall provide for the allocation of costs among the various purposes. The method used to allocate costs shall produce an equitable distribution of costs based on the relative uses or benefits provided.

(d) Administrative costs in the form of overhead or indirect costs for State central services outside of the State fish and wildlife agency must be in accord with an approved cost allocation plan and shall not exceed in any one fiscal year three percentum of the annual apportionment.

**§ 80.16 Federal aid payments.**

Payments shall be made for the Federal share of allowable costs incurred by the State in accomplishing approved projects.

(a) Requests for payments shall be submitted on forms furnished by the regional director.

(b) Payments shall be made only to the office or official designated by the State fish and wildlife agency and authorized under the laws of the State to receive public funds for the State.

(c) All payments are subject to final determination of allowability based on audit. Any overpayments made to the State shall be recovered as directed by the region director.

(d) The regional director may withhold payments pending receipt of all required reports or documentation for the project.

**§ 80.17 Maintenance.**

The state is responsible for maintenance of all capital improvements acquired or constructed with Federal Aid funds throughout the useful life of each improvement. Costs for such maintenance are allowable when provided for in approved projects. The maintenance of improvements acquired or constructed with non-Federal Aid funds are allowable costs when such improvements are necessary to accomplishment of project purposes as approved by the regional director, and when such costs are otherwise allowable by law.

**§ 80.18 Responsibilities.**

In the conduct of activities funded under the Acts, the State is responsible for:

(a) The supervision of each project to assure it is conducted as provided in the project documents, including:

(1) Proper and effective use of funds.

(2) Maintenance of project records.

(3) Timely submission of reports.

(4) Regular inspection and monitoring of work in progress.

(b) The selection and supervision of project personnel to assure that:

(1) Adequate and competent personnel are available to carry the project through to a satisfactory and timely completion.

(2) Project personnel perform the work to ensure that time schedules are met, projected work units are accomplished, other performance objectives are being achieved, and reports are submitted as required.

(c) The accountability and control of all assets to assure that they serve the purpose for which acquired throughout their useful life.

(d) The compliance with all applicable Federal, State, and local laws.

(e) The settlement and satisfaction of all contractual and administrative issues arising out of procurement entered into.

**§ 80.19 Records.**

The State shall maintain current and complete financial, property and procurement records in accordance with requirements contained in the Federal Aid Manual and OMB Circular A-102.

(a) Financial, supporting documents, and all other records pertinent to a project shall be retained for a period of three years after submission of the final expenditure report on the project. If any litigation, claim, or audit was started before the expiration of the three-year period, the records shall be retained until the resolution is completed. Records for nonexpendable property shall be retained for a period of three years following final disposition of the property.

(b) The Secretary and the Comptroller General of the United States, or any of their duly authorized representatives, shall have access to any pertinent books, documents, papers and records of the State.

**§ 80.20 Land control.**

The State must control lands or waters on which capital improvements are made with Federal Aid funds. Controls may be exercised through fee title, lease, easement, or agreement. Control must be adequate for protection, maintenance, and use of the improvement throughout its useful life.

**§ 80.21 Assurances.**

The State must agree to and certify that it will comply with all applicable Federal laws, regulations, and requirements as they relate to the application, acceptance, and use of Federal funds under the Acts. The Secretary shall have the right to review or inspect for compliance at any time. Upon determination of noncompliance, the Secretary may terminate or suspend those projects in noncompliance, or may declare the State ineligible for further participation in program benefits until compliance is achieved.

Dated: June 12, 1981.

**G. Ray Arnett,**

*Assistant Secretary for Fish and Wildlife and Parks.*

[FR Doc. 82-14203 Filed 5-24-82; 8:45 am]

BILLING CODE 4310-55-M

## DEPARTMENT OF COMMERCE

### National Oceanic and Atmospheric Administration

### 50 CFR Part 658

### Shrimp Fishery of the Gulf of Mexico

**AGENCY:** National Oceanic and Atmospheric Administration (NOAA), Commerce.

**ACTION:** Notice of closure.

**SUMMARY:** NOAA issues this notice adjusting the beginning date from June 1 to May 25 for closure of the fishery conservation zone off Texas to trawl fishing for all species except royal red shrimp. This area will remain closed through July 14. The management action is prescribed by existing regulations. The intended effect of this action is to allow harvest of brown shrimp at optimal commercial size.

**EFFECTIVE DATE:** Closure effective from 30 minutes after sunset on May 25, 1982, to 30 minutes after sunset on July 14, 1982. Public notice has been issued at least 72 hours prior to closure.

**FOR FURTHER INFORMATION CONTACT:** Jack T. Brawner, Acting Regional Director, 813-893-3141.

**SUPPLEMENTARY INFORMATION:** The Fishery Management Plan for the Shrimp Fishery of the Gulf of Mexico (FMP) provides for adjustments to the closing and opening dates for the seasonal closure of the fishery conservation zone (FCZ) off Texas. Implementing rules at 50 CFR 658.24 describe the Texas closure and specify that these adjustments be made by the Regional Director under criteria set out in that section.

Available information and estimates indicate an early closure is warranted and desirable. Biological data collected

by the Texas Parks and Wildlife Department on the size of shrimp indicate an earlier-than-usual movement of brown shrimp from the bays into the Gulf. The regulations state that the closure date must be based on a prediction of when the average size of brown shrimp leaving the bays to enter the Gulf will be 80 to 90 mm, on the strength of outgoing tides at that time, and on other ecological data. Most movement of shrimp from the bays takes place during periods of larger-than-average tidal duration, which this year occurs May 25 to 29. It is predicted that the average size of shrimp entering the Gulf of Mexico will be 90 mm on or about May 23, 1982. Based on this information, the Regional Director has determined that the customary closure dates of June 1 to July 15 will be changed to May 25 to July 14. The State of Texas will close its waters during these same days.

All trawling is prohibited between May 25 to July 14 in the area described in § 658.24(a), except that vessels may trawl for royal red shrimp beyond the 100-fathom depth contour. These vessels need no special permit or letter of authorization.

This action is taken under the authority of 50 CFR 658.24, and is taken in compliance with Executive Order 12291. (16 U.S.C. 1801 *et. seq.*)

**List of Subjects in 50 CFR Part 658**

Fish, Fisheries.

Dated: May 19, 1982.

Robert K. Crowell,

*Deputy Executive Director, National Marine Fisheries Service.*

[FR Doc 82-14218 Filed 5-24-82; 8:45 am]

BILLING CODE 3510-22-M

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Part 444

**[Docket No. 80N-0187; DESI 8674]**

## Neomycin Sulfate-Sodium Propionate Otic Solution; Termination of Stay of Effective Date of a Final Rule Revoking Certification

**AGENCY:** Food and Drug Administration.

**ACTION:** Final rule; termination of stay.

**SUMMARY:** The Food and Drug Administration (FDA) is terminating the stay of the effective date of a final rule revoking the provisions for the certification of neomycin sulfate-sodium propionate otic solution. The basis for the revocation was that the drug product lacked substantial evidence of effectiveness. The effective date of the final rule was stayed pending review of a hearing request which has now been withdrawn.

**EFFECTIVE DATE:** May 26, 1982.

**FOR FURTHER INFORMATION CONTACT:** Douglas I. Ellsworth, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** In the **Federal Register** of September 19, 1974 (39 FR 33665), FDA published a final rule revoking § 444.442a (21 CFR 444.442a), which provided for the certification of neomycin sulfate-sodium propionate otic solution. The basis for the final rule was that the drug product lacked substantial evidence of effectiveness. The revocation was to take effect on October 29, 1974, unless a hearing was requested on the revocation. The final rule stated that if a hearing was requested, the effective date would be extended to allow for review of the hearing request.

In response, a hearing was requested for the following drug product:

NDA 50-364; Otobiotic Otic Solution containing neomycin sulfate and sodium propionate; Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033.

Accordingly, in a notice published in the **Federal Register** of March 14, 1975 (40 FR 11870), as amended by a notice published November 4, 1980 (45 FR 73034), FDA stayed the order revoking the portion of § 444.442a that provides for neomycin sulfate-sodium propionate otic solution.

Subsequently, Schering Corp. reformulated Otobiotic Otic Solution to an effective drug product containing polymyxin B sulfate and hydrocortisone (certified under 21 CFR 448.430), received FDA's approval of the new formulation, and withdrew its hearing request concerning the revocation of § 444.442a.

Therefore, under the Federal, Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-1051 as amended, 59 Stat. 463 as amended (21 U.S.C. 352, 357)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)) and redelegated to the Director, Bureau of Drugs (21 CFR 5.78), notice is given that the September 19, 1974 revocation, the effective date of which was extended by the March 14, 1975 notice, as amended by the November 4, 1980 notice, is effective May 25, 1982. All outstanding certificates for neomycin sulfate-sodium propionate otic solution are revoked and the regulation under which they were issued (21 CFR 444.442a) is revoked. No new certificates will be issued.

(Secs. 502, 507, 52 Stat. 1050-1051 as amended, 59 Stat. 463 as amended (21 U.S.C. 352, 357))

Dated: April 16, 1982.

J. Richard Crout,

*Director, Bureau of Drugs.*

[FR Doc. 82-13902 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

# Proposed Rules

Federal Register
Vol. 47, No. 101
Tuesday, May 25, 1982

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

## DEPARTMENT OF AGRICULTURE

### Agricultural Marketing Service

### 7 CFR Part 1106

### Milk in the Oklahoma Metropolitan Marketing Area; Proposed Suspension of Certain Provisions of the Order

**AGENCY:** Agricultural Marketing Service, USDA.

**ACTION:** Proposed suspension of rules.

**SUMMARY:** This notice invites written comments on a proposal to continue for an additional month a suspension of certain provisions of the Oklahoma Metropolitan Federal milk order. The proposed suspension, which would apply to June 1982, would reduce the amount of milk that a supply plant must ship to pool distributing plants in order to qualify as a pool plant. Also, the proposed action would increase the amount of milk that may be moved directly from farms to nonpool plants for manufacturing and still be priced under the order. The continuation of the earlier suspension for April and May was requested by a producer cooperative association because it is anticipated that milk production will continue to be considerably in excess of fluid milk sales in June.

**DATE:** Comments are due not later than June 1, 1982.

**ADDRESS:** Comments (two copies) should be filed with the Hearing Clerk, Room 1077, South Building, U.S. Department of Agriculture, Washington, D.C. 20250.

**FOR FURTHER INFORMATION CONTACT:** Robert F. Groene, Marketing Specialist, Dairy Division, Agricultural Marketing Service, U.S. Department of Agriculture, Washington, D.C. 20250, (202) 447–4824.

**SUPPLEMENTARY INFORMATION:** This proposed action has been reviewed under USDA procedures established to implement Executive Order 12291 and has been classified "not significant" and, therefore, not a major action.

It has been determined that any need for suspending certain provisions of the order on an emergency basis precludes following certain review procedures set forth in Executive Order 12291. Such procedures would require that this document be submitted for review to the Office of Management and Budget at least 10 days prior to its publication in the **Federal Register.** However, this would not permit the completion of the required suspension procedures in time for the suspension to be continued for June 1982 deliveries if this is found necessary. The initial request for this action was received on May 17, 1982.

It also has been determined that this proposed action would not have a significant economic impact on a substantial number of small entities. Such action would lessen the regulatory impact of the order on certain milk handlers and would tend to ensure that dairy farmers would continue to have their milk priced under the order and thereby receive the benefits that accrue from such pricing.

Notice is hereby given that, pursuant to the provisions of the Agricultural Marketing Agreement Act of 1937, as amended (7 U.S.C. 601 *et seq.*), the suspension of the following provisions of the order regulating the handling of milk in the Oklahoma Metropolitan marketing area is being considered for the month of June 1982.

**§ 1106.7 [Temporarily suspended in part]**

1. In § 1106.7(b), that part of the provisions that reads "until any month of such period in which less than 20 percent of the plant receipts and diverted milk specified previously herein is transferred to plants described in paragraph (a) of this section. A plant not meeting such 20 percent requirement in any month of such January–August period shall be qualified under this paragraph in any remaining month of the year only if transfers of fluid milk products (except filled milk) from the plant during the month to plant(s) described in paragraph (a) of this section are at least 50 percent of the plant receipts and diverted milk specified previously herein".

**§ 1106.13 [Temporarily suspended in part]**

2. In § 1106.13(e)(1), that part of the provisions that reads ", subject to the conditions of paragraph (e)(3) of this section, a total quantity of milk not in excess of total" and "received at all pool plants during the month. Diversions in excess of such quantity shall not be eligible under this section and the diverting cooperative shall specify the dairy farmers whose diverted milk is not so eligible. If the cooperative association fails to designate such persons, status under this section shall be forfeited with respect to all milk diverted by such cooperative association".

3. In § 1106.13(e)(2), that part of the provisions that reads ", subject to the conditions of paragraph (e)(3) of this section," and ", in a total quantity not in excess of the milk of producers not members of such cooperative association received at such pool plant(s) during the month. Milk diverted in excess of such quantity shall not be eligible under this section and the diverting handler shall specify the dairy farmers whose diverted milk is not so eligible. If a handler fails to designate such persons, status under this section shall be forfeited with respect to all milk diverted by such handler".

4. In § 1106.13, paragraph (e)(3).

All persons who desire to submit written data, views, or arguments in connection with the proposed suspension should file two copies of such material with the Hearing Clerk, Room 1077, South Building, United States Department of Agriculture, Washington, D.C. 20250, not later than June 2, 1982. The period for filing comments is limited to 7 days because a longer period would not permit the completion of the required suspension procedures in time for the suspension to be made effective for the month of June 1982.

The comments that are sent will be available for public inspection at the office of the Hearing Clerk during regular business hours (7 CFR 1.27(b)).

**Statement of Consideration**

The proposed suspension would continue for the month of June an identical suspension that was effective for April and May 1982. Under the proposed suspension, the amount of milk that supply plants must ship to pool distributing plants to attain pool plant status would be reduced in that only one shipment to a pool distributing plant would be needed to pool a supply plant. Also, the proposed action would increase the amount of milk that may be moved directly from farms to nonpool manufacturing plants and still be priced

under the order. Without the suspension, diversions would be limited to producers who deliver not less than 15 percent of their producer milk to pool plants. In addition, diversions to nonpool plants by proprietary handlers and cooperatives could not exceed the quantity of producer milk received at pool plants.

A continuation of the suspension was requested by a cooperative association that represents producers who supply the market. The cooperative indicated that the same imbalance between fluid requirements and production that existed in April and May is expected to continue in June. The cooperative stated that, although milk production appears to have reached its peak, there appears to be no indication of a decrease in production. Consequently, the cooperative anticipates that milk production will hold close to present levels well into June while fluid milk sales in June are expected to be below April and May levels due to schools being closed. Thus, the cooperative anticipates that greater than normal quantities of milk will have to be moved to manufacturing outlets for surplus disposal. In the absence of a continuation of the current suspension for the month of June, the cooperative contends that it would be necessary to make costly and inefficient movements of milk solely for the purpose of pooling the milk of dairy farmers who have regularly supplied the fluid milk needs of the market.

**List of Subjects in 7 CFR Part 1106**

Milk marketing orders, Milk, Dairy products.

Signed at Washington, D.C. on: May 20, 1982.

**William T. Manley,**

*Deputy Administrator, Marketing Program Operations.*

[FR Doc. 82-14231 Filed 5-24-82; 8:45 am]

BILLING CODE 3410-02-M

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

### 21 CFR Parts 172 and 189

**[Docket No. 81N-0292]**

## Cinnamyl Anthranilate; Proposed Prohibition of Use in Human Food

**AGENCY:** Food and Drug Administration.

**ACTION:** Proposed rule.

**SUMMARY:** The Food and Drug Administration (FDA) is proposing to prohibit the use of cinnamyl anthranilate in human food. The proposal is based on a National Cancer Institute (NCI) study indicating that ingestion of cinnamyl anthranilate causes cancer in mice. The proposal would remove cinnamyl anthranilate from the list of food additives for direct addition to food for human consumption and would list cinnamyl anthranilate as a substance prohibited from use in food.

**DATE:** Comments by July 26, 1982.

**ADDRESS:** Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

**FOR FURTHER INFORMATION CONTACT:** Donna A. Dennis, Bureau of Foods (HFF-335), Food and Drug Administration, 200 C St., SW., Washington, D.C. 20204, 202-472-4750.

**SUPPLEMENTARY INFORMATION:** Cinnamyl anthranilate ($C_{16}H_{15}NO_2$, CAS Reg. No. 87-29-6) is the ester of cinnamyl alcohol and anthranilic acid. It has been used since the 1940's in food and cosmetics as a component of imitation grape or cherry flavors and as a fragrance ingredient. In 1977, the U.S. International Trade Commission (Ref. 1) reported that the total U.S. sales of cinnamyl anthranilate in 1976 for use as a flavoring and as a fragrance ingredient was 2,000 pounds. In 1973, the National Academy of Sciences/National Research Council (NAS/NRC) (Ref. 2) reported that in 1970 approximately 700 pounds of cinnamyl anthranilate were used for flavoring food. The use of cinnamyl anthranilate in various food categories was reported by (1) the 1970 NAS/NRC survey (published in 1973) (Ref. 3) and (2) Hall and Oser (Ref. 4) as follows:

| Food category | Use level (parts per million) | |
|---|---|---|
| | NAS/NRC survey | Hall and Oser |
| Baked goods | 26 | 5.3 |
| Frozen dairy | 14 | 1.7 |
| Soft candy | 28 | 4.3 |
| Gelatins, puddings, and fillings | 32 | 28 |
| Alcoholic beverages and bases | 15 | (1) |
| Nonalcoholic beverages | 7 | 6.8 |
| Hard candy | 7 | (1) |
| Chewing gum | (1) | 46-730 |
| Miscellaneous, unclassified | 1 | (1) |

[1] None reported.

Cinnamyl anthranilate is listed as a direct food additive in § 172.515 *Synthetic flavoring substances and adjuvants* (21 CFR 172.515). This regulation was published in the **Federal Register** of October 27, 1964 (29 FR 14625) as 21 CFR 121.1164. In addition, in 1965, the Flavor Extract Manufacturers Association (FEMA) published a list of flavoring ingredients (Ref. 4), including cinnamyl anthranilate, that it considered to be generally recognized as safe for addition to food for human consumption. This list was based on two preliminary lists published by FEMA in 1960 and 1961.

The evidence used in 1964 to support the safe use of cinnamyl anthranilate in food included its previous history of use in food, the presence of other cinnamyl and anthranilate derivatives naturally in food and in natural substances used to flavor food, and some toxicological data, primarily acute toxicity data, to support the safety of some of these derivatives.

Recent studies on cinnamyl anthranilate include a study by Stoner et al. (Ref. 5) reporting that intraperitoneal administration of cinnamyl anthranilate produced primary lung tumors in a 24-week mouse pulmonary tumor response system. Following publication of this study, several short-term studies were performed in which cinnamyl anthranilate exhibited (1) low acute toxicity (its $LD_{50}$ in rats was greater than 5 g/kg body weight) (Ref. 6); (2) no mutagenicity in a bacterial assay (Ref. 7); and (3) no teratogenicity in a chicken embryo assay (Ref. 8). Cinnamyl anthranilate was selected for testing under the National Cancer Institute's Carcinogenesis Testing Program because of its use as a direct food additive and because of the results of the Stoner study. The National Institutes of Health issued a notice in the **Federal Register** of December 30, 1980 (45 FR 85832), announcing completion of the study and the public availability of the NCI bioassay report for cinnamyl anthranilate.

In the NCI report, "Bioassay of Cinnamyl Anthranilate for Possible Carcinogenicity" (Ref. 9), the results of this bioassay were summarized as follows:

A bioassay of cinnamyl anthranilate (a synthetic flavoring agent) for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats and 50 mice of each sex were fed the test chemical in diets containing 15,000 or 30,000 ppm for 103 weeks and then observed for an additional 2 or 3 weeks. Controls consisted of groups of 50 untreated rats and 50 untreated mice of each sex. All surviving animals were killed and necropsied at 105 to 107 weeks.

Mean body weights of the dosed male and female rats and mice were lower than those of the corresponding controls throughout the bioassay and weight decrements were dose related. Mortality in rats or mice of either sex was not affected by administration of the test chemical.

In male rats, adenocarcinomas or adenomas of the renal cortex and acinar-cell

carcinomas or adenomas of the pancreas were found in low incidences in dosed rats but not in control rats. In direct comparisons with matched control groups, the incidences of these tumors were not significantly increased; however, because these tumors rarely occur spontaneously in aging F344 rats, they were considered to be related to compound administration. Similar pancreatic or renal tumors have not been detected among 634 historical-control male F344 rats at the same laboratory.

In the female rats, no tumors occurred at incidences that could be clearly related to administration of the test chemical.

In both male and female mice, the incidences of hepatocellular carcinomas or adenomas were dose related (P less than 0.001) and significant (P less than or equal to 0.001) in direct comparisons of dosed and control groups.

It was concluded that under the conditions of this bioassay cinnamyl anthranilate was carcinogenic for male and female B6C3F1 mice, inducing increased incidences of hepatocellular carcinomas or adenomas. The test chemical was also carcinogenic for male F344 rats, inducing low incidences of acinar-cell carcinomas or adenomas of the pancreas and adenocarcinomas or adenomas of the renal cortex. Cinnamyl anthranilate was not carcinogenic for female F344 rats.

A copy of the National Cancer Institute's report, along with other information referenced in this document, has been placed on public display in the Dockets Management Branch (address above) and may be seen between 9 a.m. and 4 p.m., Monday through Friday.

The FDA Bureau of Foods' Cancer Assessment Committee (CAC) reviewed the reported NCI studies on the possible carcinogenicity of cinnamyl anthranilate in rats and mice. In its report (Ref. 10), the CAC notes that, in the mouse study, cinnamyl anthranilate induced a significant increase in the incidence of hepatocellular adenomas and carcinomas in both the male and female. The CAC concludes that these data, together with the presence of liver hyperplastic lesions in treated but not control animals, the shorter latency period for the onset of liver tumors in the treated groups, and the higher degree of malignancy of the tumors in treated groups, provide a convincing case for the carcinogenicity of cinnamyl anthranilate in mice.

The CAC notes, however, that in the rat study, there were no statistically significant increases in tumor incidence in treated groups compared to the controls. The CAC further notes that, in the high dose group, small increases occurred in the number of males bearing tumors at sites infrequently displaying spontaneous neoplastic lesions. The CAC considers that the presence of these tumors may be associated with compound treatment, but that the evidence is suggestive rather than conclusive.

As a result of this evaluation of the NCI study, the agency has concluded that cinnamyl anthranilate is carcinogenic to male and female B6C3F1 mice because it induces ademonas and carcinomas of the liver. The agency also has concluded that the small increases in the incidence of tumors of the kidney and pancreas in male F344 rats may also be related to treatment by cinnamyl anthranilate, but that conclusive evidence of this association is currently lacking.

Section 402(a)(2)(C) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 342(a)(2)(C)) defines a food as adulterated "if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 409." Section 409(a) of the act (21 U.S.C. 348(a)) states that a food additive shall be deemed to be unsafe unless "there is in effect, and it and its use or intended use are in conformity with, a regulation issued under this section prescribing the conditions under which such additive may be safely used." In addition, section 409(c)(3)(A) of the act states that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal * * *." On the basis of its analysis of the NCI report, FDA has concluded that cinnamyl anthranilate is a carcinogen when ingested by test animals. Therefore, the agency has concluded that cinnamyl anthranilate connot be approved as a food additive. Accordingly, under section 409 of the act, the agency is proposing to remove the listing of cinnamyl anthranilate in § 172.515 and is proposing a new regulation for cinnamyl anthranilate in Part 189 (21 CFR Part 189). Under this proposal, the addition of cinnamyl anthranilate to food would cause the food to be adulterated within the meaning of section 402(a) of the act and would subject the food to regulatory action. The agency expects to issue the appropriate final rule at the earliest possible date following the close of the comment period.

The agency concludes, however, that the protection of the public health does not require the recall of food (including intermediates) containing cinnamyl anthranilate from the market, or the destruction of food to which the substance has already been added. The agency has calculated an upper limit estimate of the risk presented by human ingestion of cinnamyl anthranilate at current levels of use. The agency utilized a linear proportional model, using the upper 99 percent confidence interval of the observed tumor incidence, as described in FDA's March 20, 1979 proposal, "Chemical Compounds in Food-Producing Animals" (44 FR 17070). According to this assessment, the upper limit of lifetime risk of cancer from ingestion of cinnamyl anthranilate at its previously reported levels of use is less than 1 in a million.

There are no fixed criteria for deciding whether to recall a product; each case must be judged on its own facts. The estimated risk cinnamyl anthranilate is low. Therefore, the agency believes that it is appropriate to permit the depletion of stocks of food products (including intermediates) containing cinnamyl anthranilate that were manufactured before the effective date of the final regulation.

The agency has carefully considered the potential environmental effects of this proposed action and has concluded that the action will not have a significant impact on the human environment. Therefore, an environmental impact statement is not required. The agency's findings of no significant impact and its environmental assessment may be seen in the Dockets Management Branch (address above), between 9 a.m. and 4 p.m., Monday through Friday.

In accordance with the Regulatory Flexibility Act (Pub. L. 96–354), FDA has considered the effect that this regulation would have on small entities, including small businesses. The agency has determined that, although the proposed regulation would remove an approved additive from food, the effect of this action on small entities will be minimal. Only small amounts of cinnamyl anthranilate are currently used in food, and reformulation costs would be minimal because substitute ingredients are readily available. In addition, the agency has proposed no recall or destruction of products containing cinnamyl anthranilate that were manufactured before the effective date of the final regulation. The agency certifies that the publication of this proposal will not have a significant economic impact on a substantial number of small entities.

A decision on what, if any, regulatory

action should be taken on the use of cinnamyl anthranilate as an ingredient of drug and cosmetic products is being deferred until completion of the evaluation of skin penetration studies conducted by FDA and consideration of the total exposure to cinnamyl anthranilate from its use in these products.

References

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

1. United States International Trade Commission (1977), *Synthetic Organic Chemicals—United States Production and Sales, 1976*, USITC Publication 833, U.S. Government Printing Office, Washington, DC.

2. National Academy of Sciences/National Research Council (1973), *A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe:* Table 11: Part C—Annual Poundage Data for FEMA Questionnaire Substances Not Listed in NAS Appendix A (Group III). National Technical Information Service, Springfield, VA, Order No. PB 221-936.

3. National Academy of Sciences/National Research Council (1973), *A Comprehensive Survey of Industry on the Use of Food Chemicals Generally Recognized as Safe:* Table: Maximum Usage Levels Reported in NAS-GRAS Phase II Survey—by Substance, Food Category, and Technical Effects, Group B: FEMA Questionnaire Substances not in Appendix A.

4. Hall, R. L. and B. L. Oser, "Recent Progress in the Consideration of Flavoring Ingredients under the Food Additives Amendment. III. GRAS Substances," *Food Technology*, 19:151-197, 1965.

5. Stoner, G. D., M. B. Shimkin, A. J. Kniazeff, J. H. Weisburger, E. K. Weisburger, G. B. Gori, "Test for Carcinogenicity of Food Additives and Chemotherapeutic Agents by the Pulmonary Tumor Response in Strain A Mice," *Cancer Research*, 13:751-752, 1973.

6. Opdyke, D. L. J., "Cinnamyl Anthranilate," *Food and Cosmetics Toxicology*, 13:751-752, 1975.

7. Litton Bionetics, Inc. (1975), *Mutagenic Evaluation of Compound FDA 73-59 Cinnamyl Anthranilate.*

8. Food and Drug Administration (1976), "Investigations of the Toxic and Teratogenic Effects of GRAS Substances to the Developing Chicken Embryo: Cinnamyl Anthranilate."

9. National Cancer Institute (1980), "Bioassay of Cinnamyl Anthranilate for Possible Carcinogenicity," Technical Report No. 196, DHEW Publication No. (NIH) 80-1752, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD.

10. Cancer Assessment Committee, Bureau of Foods, Food and Drug Administration (1980). Memorandum of meeting, "Cinnamyl anthranilate."

List of Subjects in 21 CFR

*Part 172*

Food additives; Food preservatives; Spices and flavorings.

*Part 189*

Food ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act (Secs. 201(s), 402, 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 342, 348, 371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1; see 46 FR 26052; May 11, 1981)), it is proposed that Parts 172 and 189 be amended as follows:

## PART 172—FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

**§ 172.515 [Amended]**

1. Part 172 is amended in § 172.515 *Synthetic flavoring substances and adjuvants* by removing the entry for "cinnamyl anthranilate".

## PART 189—SUBSTANCES PROHIBITED FROM USE IN HUMAN FOOD

2. Part 189 is amended by adding new § 189.113 to read as follows:

**§ 189.113 Cinnamyl anthranilate.**

(a) The food additive cinnamyl anthranilate ($C_{16}H_{15}NO_2$, CAS Reg. No. 87-29-6) is the ester of cinnamyl alcohol and anthranilate acid. Cinnamyl anthranilate is a synthetic chemical that has not been identified in natural products at levels detectable by available methodology. It has been used as a flavoring agent in food.

(b) Food containing any added cinnamyl anthranilate is deemed to be adulterated in violation of the act based upon an order published in the **Federal Register** of (insert date and reference for publication of the final rule).

Interested persons may, on or before July 26, 1982 submit to the Dockets Management Branch (address above), written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: April 13, 1982.

**Arthur Hull Hayes, Jr.,**

*Commissioner of Food and Drugs.*

[FR Doc. 82-14165 Filed 5-24-82; 8:45 am]

BILLING CODE 4160-01-M

## 21 CFR Part 452

**[Docket No. 79N-0459]**

## Erythromycin Estolate: Withdrawal of Proposal to Revoke Provisions for Certification of Tablets and Capsules; Response to Petition; Labeling

**AGENCY:** Food and Drug Administration.

**ACTION:** Withdrawal of proposed rule.

**SUMMARY:** The Commissioner of Food and Drugs announces that he has completed his review of the administrative record concerning the safety of erythromycin estolate. The Commissioner concludes that the drug is safe in that the risks of hepatotoxicity do not outweight its therapeutic benefits. Accordingly, the Commissioner withdraws a proposal to revoke provisions for certification of adult dosage forms of erythromycin estolate and in a related document published elsewhere in this issue sets forth the labeling changes. In addition, the Commissioner denies a petition requesting that all dosage forms of erythromycin estolate be removed from the market.

**DATES:** Withdrawal of the proposal to revoke provisions for certification is effective May 25, 1982.

**ADDRESS:** The transcript of the public hearing before the advisory committee, evidence and comments submitted, and all other documents listed in this notice may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

**FOR FURTHER INFORMATION CONTACT:** Suzanne O'Shea, Bureau of Drugs (HFD-32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

**SUPPLEMENTARY INFORMATION:** This notice withdraws the proposal of the Director of the Bureau of Drugs to revoke provisions for certification of adult dosage forms of erythromycin estolate (tablets—21 CFR 452.115a, capsules—21 CFR 452.115b). The basis of the proposal was that erythromycin estolate is unsafe because of the risks of hepatotoxicity (adverse liver effects) associated with its use, particularly in light of the availability of other erythromycins indicated for the same conditions which do not cause hepatotoxicity. The proposal described new evidence suggesting that the estolate may be less bioavailable than other erythromycins. In addition, the proposal asserted that there are no other significant therapeutic benefits peculiar

to the estolate which would justify its continued certification. Thus, the proposal asserted that the risks of the drug had been tentatively found to outweigh its benefits. The effect of the Director's proposal, if finalized, would have been removal of adult forms of erythromycin estolate from the market.

This notice also denies a petition submitted by Health Research Group (HRG), a consumer-oriented organization interested in the regulation of drugs. Using a rationale similar to the Director's, the petitioner requested that all dosage forms of erythromycin estolate be removed from the market. This request included the pediatric dosage forms: oral suspension, pediatric drops, and chewable tablets.

The Commissioner has reviewed data submitted by the manufacturers of erythromycin estolate, HRG, and the Bureau of Drugs (Bureau). He has reviewed the presentations made at a public hearing before the Ad Hoc Advisory Committee on Erythromycin Estolate (Committee). In addition, the Commissioner has considered the 763 comments that were submitted on the proposal.

The Committee found that, for adult and pediatric dosage forms of erythromycin estolate, the risks do not outweigh the benefits. The Commissioner accepts the Committee's recommendations which state that both adult and pediatric dosage forms of the estolate have a favorable risk/benefit ratio. Specifically, he concludes that the estolate is associated with a higher incidence of hepatotoxicity than other erythromycins, but this risk is offset by more reliable initial absorption, which may be important in serious infections, and by lack of significant effect of food on absorption.

## I. Introduction

### *A. The Drug*

Erythromycins belong to the macrolide group of antibiotics. They are alternative therapy for certain treatment and prophylaxis of diseases in patients allergic to penicillin. Erythromycins are also used in the treatment of Legionnaire's disease, pertussis, diptheria, intestinal amebiasis, primary syphilis, upper and lower respiratory tract infections, skin and soft tissue infections caused by susceptible organisms.

There are four types of erythromycin in solid dosage form currently available: erythromycin base, erythromycin ethyl succinate, erythromycin stearate, and erythromycin estolate. Erythromycin base, the original erythromycin formulation, was discovered in 1952. Gastric acidity has an inactivating effect on erythromycin base. Many erythromycin base products are, therefore, coated to help prevent inactivation. The stearate salt and the ethyl succinate ester of erythromycin were developed a few years later, in an attempt to overcome the problem of absorption associated with the base.

Erythromycin estolate was formulated in the late 1950's in an attempt to provide a form of erythromycin that would be more reliably absorbed than the base, stearate, or ethyl succinate. It is the lauryl sulfate salt of the propionyl ester of erythromycin base. Because of acid stability, it is not inactivated by gastric juices. After oral administration, erythromycin estolate is in the blood as free erythromycin base and as propionyl erythromycin ester. The propionyl ester hydrolyzes to the free base form of erythromycin.

Dista Products Co., Division of Eli Lilly & Co., P.O. Box 1407, Indianapolis, IN 46206 (Lilly) is the major producer of erythromycin estolate. The antibiotic forms (applications) for Lilly's adult dosage forms currently marketed tablets and capsules are numbered 61–896; 500 mg tablets, and 61–897; 125 mg and 250 mg capsules. The trade name for its erythromycin estolate products is Ilosone. Most of the studies presented and reviewed were conducted with Ilosone. This notice refers to erythromycin estolate rather than Ilosone, however, because the data pertain to all brands of estolate.

Erythromycin estolate capsules (250 mg) are also currently marketed by Danbury Pharmacal Inc., 131 West St., P.O. Box 296, Danbury, CT 06810, under antibiotic form 62–087.

Since the hearing before the Committee, FDA has approved the applications of two additional manufacturers:

1. 62–162; 125 mg and 250 mg capsules, Barr Laboratories, Inc., 265 Livingston St., Northvale, NJ 07647.

2. 62–237; 250 mg capsules, Zenith Laboratories, 140 LeGrand Ave., Northvale, NJ 07647.

### *B. Regulatory History*

Erythromycin estolate was first approved for marketing in 1958. It was one of the drugs reviewed in the Drug Efficacy Study. In the **Federal Register** of August 29, 1970 (35 FR 13803), October 14, 1971 (36 FR 19988), and September 17, 1976 (41 FR 40209), the agency classified the drug as effective in the treatment of various infections.

The hepatic potential of the estolate has been of concern to the agency for many years. The first report of hepatotoxicity associated with the estolate was published in 1961. In 1962, the package insert was revised to add information about the recognized hepatotoxicity with the estolate. The firm sent two "Dear Doctor" letters to health professionals concerning the hepatotoxicity of the estolate—one in 1961, the second in 1963.

1. *The 1973 action.* In April 1973, HRG submitted a petition requesting that all dosage forms of erythromycin estolate be withdrawn from the market. The petition stated that the estolate causes serious hepatic effects not caused by other erythromycins without conferring any offsetting advantage.

In May 1973, FDA's Anti-Infective Advisory Committee met to discuss the safety and effectiveness of erythromycin estolate. The Committee found that hepatotoxicity was associated only with the estolate, not the other forms of erythromycin. It found, however, that when given in lower doses, the estolate was an effective as other erythromycins for streptococcal infections and primary syphilis (Refs. 12, 13, and 71). The Committee rejected the sore throat study submitted by HRG in which the estolate, stearate, and ethyl succinate were equally effective because no microbiological confirmation of etiology was made (Ref. 128).

Thus, the Committee concluded that the estolate's higher blood levels had been correlated with greater effectiveness, and that the estolate's risk/benefit ratio was favorable. The Committee also concluded that children appear to be immune to estolate toxicity. It recommended to FDA that the safety of adult dosage forms of erythromycin estolate did not warrant removing them from the market, but also recommended that the hepatotoxicity warning be strenghtened in the estolate labeling. The Commissioner accpeted the Committee's findings and, as a consequence, the package insert for erythromycin estolate was revised again, this time to include a boxed warning of its hepatotoxic potential.

2. *The 1979 Action.* In 1978, the Bureau obtained new data indicating that the blood levels of free erythromycin base may be actually lower than for the estolate than for other erythromycins. In addition, upon review of FDA's file of nationwide spontaneously reported adverse drug reactions (ADR reports), it appeared that of the reports of hepatotoxicity due to some oral erythromycin product, 93 percent had hepatotoxicity associated with the estolate, a proportion much greater than the estolate's market share. Further, the Bureau knew of no studies indicating that the estolate is clinically more

effective than other erythromycins. Thus, it appears that the greater hepatoxicity of erythromycin estolate was not counterbalanced by greater bioavailability of clinical effectiveness, and on a benefit/risk basis the estolate was less safe than other forms of erythromycin.

By letter of August 29, 1979, the agency requested that Lilly voluntarily remove all dosage forms of the drug from the market. The agency made the same request of Danbury by letter dated September 10, 1979. In response to the letters, Lilly asserted that erythromycin estolatge is safe and effective, and declined to voluntarily withdraw the products from the market. Danbury responded that the estolate is safe and effective, but stated that if the estolate were demonstrated to be unsafe, it would voluntarily withdrew it from the market.

On August 30, 1979, HRG submitted a second petition requesting the withdrawal from the market of all dosage forms of erythromycin estolate. Again, the basis of the petition was that the estolate causes hepatic reactions not caused by other erythromycins, and that there is no offsetting advantage to the estolate.

In the **Federal Register** of December 4, 1979 (44 FR 69670), the Director of the Bureau of Drugs proposed to revoke the provisions for certification of adult dosage forms of erythromycin estolate, stating that the drug appears to cause significantly more hepatic reactions, is less bioavailable, and is clinically no more effective than other erythromycins. The notice stated that comments would be accepted until January 3, 1980.

The pediatric dosage forms (chewable tablets, pediatric drops, and oral suspensions) were not included in the proposal. From the data available it appeared that the prevalence of hepatic reactions in young children is much less than in adults. Further, it was not clear that the number of hepatic reactions in relation to usage in young children was different for the different salts and esters of erythromycin.

The December 4, 1979 proposal stated that interested persons could submit a request for an informal conference on the proposed revocation. The agency received one request for an informal conference and two requests for an extension of the comment period. In the **Federal Register** of January 4, 1980 (45 FR 1085), the Director announced that because of the controversial nature of the proposal, he would grant the request for an informal conference. The comment period was extended to February 4, 1980.

The informal conference was held on January 18, 1980. At the conference, presentations were made by Lilly, Barr Laboratories, and two individuals. A transcript of the conference may be seen at the Dockets Management Branch under docket number 79N–0459.

*C. The Ad Hoc Committee on Erythromycin Estolate*

In order to assure that the factors determining the risks and benefits of erythromycin estolate were as fully developed as possible before a final determination was made, the agency decided to submit the substantive issues to an independent scientific review by an advisory committee. Because the charter of the appropriate standing advisory committee has expired, the Commissioner chartered, in the **Federal Register** of June 10, 1980 (45 FR 39340), the Ad Hoc Advisory Committee on Erythromycin Estolate (Committee) to review information pertaining to adult and pediatric dosage forms of erythromycin estolate and to advise the agency on the determination of the benefit/risk ratio of all dosage forms.

In a notice published in the **Federal Register** of February 27, 1981 (46 FR 14355), the Commissioner announced that a public hearing before the Ad Hoc Committee would be held on April 16–17, 1981. The Commissioner asked manufacturers, the Bureau of Drugs, and other interested persons to make written submissions of data for consideration by the Committee, and to be prepared to make oral presentations at the hearing. The Commissioner also set out the specific issues to be considered by the Committee:

1. Whether the prevalence of adverse liver effects from erythromycin estolate is greater for adults or children, or both, than that for other erythromycins; if so, whether the difference is clinically significant.

a. Whether voluntary adverse drug reaction reports can reliably be used to determine the relative prevalence of adverse liver effects for erythromycins; if so, what differences they show in the relative prevalence of those effects and whether the differences are clinically significant.

b. Whether data that are presented from the Kaiser-Permanente Study, or from any other retrospective study, can reliably by used to determine the relative prevalence of adverse liver effects for erythromycins; if so, what differences the data show in the relative prevalence of those effects and whether the differences are clinically significant.

c. Whether data that are presented from any prospective clinical study can reliably be used to determine the incidence of adverse liver effects for erythromycins; if so, what differences the data show in the relative incidence of those effects and whether the differences are clinically significant.

2. Whether there are any differences among erythromycins in the prevalence of adverse effects in adults or in children, or both, other than those involving the liver (for example, gastrointestinal intolerance); if so, whether those differences are clinically significant. Please state the basis for your conclusions.

3. For every bioavailability/bioequivalence study that is presented, the Committee is asked to comment on the adequacy of the design for determining bioavailability/bioequivalence, and whether the Committee believes the results of the study can be relied on to draw conclusions about comparative bioavailability of erythromycins under actual conditions of medical practice. The Committee will also address the following questions:

a. Whether tissue concentration studies of erythromycin estolate and erythromycin ethylsuccinate provide any evidence of clinically significant advantage for adults or children. Please identify the specific studies on which your conclusions are based.

b. Whether studies showing observable higher blood levels of erythromycin as the estolate indicate that erythromycin estolate is more reliably absorbed than other erythromycins and whether the studies provide any evidence of clinically significant advantage for adults or children. Please identify the specific studies on which your conclusions are based.

c. Whether erythromycin estolate, measured as the base, provides higher, the same, or lower blood levels that other erythromycins measured as the base; whether, as so measured, erythromycin estolate is more, equally, or less reliably absorbed than other erythromycins; and whether the differences, if any, are clinically significant. Please identify the specific studies on which your conclusions are based.

4. Whether the propionyl ester of erythromycin estolate, apart from its being hydrolyzed, contributes to the therapeutic effect of erythromycin estolate; if so, why. Does it, for example, have an antibacterial effect? Whether, if the propionyl ester contributes to the therapeutic effect of erythromycin estolate, it has been demonstrated to convey a clinical advantage over other

erythromycins. Please state the basis for your conclusion.

5. Whether a prospective study to determine the therapeutic effect (for example, antimicrobial) of the propionyl ester portion of the estolate molecule is feasible and needed; if so, what the design of such a study should be.

6. Whether erythromycin estolate has been shown in clinical practice to offer any therapeutic advantage in adults or children over other erythromycins.

a. Whether erythromycin estolate has been shown to be effective at lower doses than other erythromycins in the treatment of streptococcal infections and primary syphilis; if so, whether this use of lower doses offers any clinical advantage. Please state the basis for your conclusion.

b. Whether erythromycin estolate has been shown to be more effective than erythromycin ethylsuccinate in the treatment of *Haemophilus influenzae* otitis media. Please state the basis for your conclusion.

c. Whether erythromycin estolate has been shown to have any advantage over other erythromycins in the treatment of diphtheria, pertussis, Legionnaires disease, chlamydial infections, and *Campylobacter* enteritis. Please state the basis for your conclusion.

7. On the basis of the evidence presented, whether erythromycin estolate has a better, the same, or a poorer benefit/risk ratio in adults than other available erythromycins. Please state the basis for your conclusion.

8. If erythromycin estolate has a favorable risk/benefit ratio in adults, what labeling changes, if any, are recommended for adult dosage forms of erythromycin estolate.

9. On the basis of the evidence presented, whether erythromycin estolate has a better, the same, or a poorer benefit/risk ratio in children than erythromycin ethylsuccinate. Please state the basis for your conclusion.

10. If erythromycin estolate has a favorable risk/benefit ratio in children when compared to erythromycin ethylsuccinate, what labeling changes, if any, are recommended for pediatric dosage forms of erythromycin estolate.

The Committee's report was submited on July 24, 1981. In order to allow public comment on the Committee's report, the comment period was extended by notice published in the **Federal Register** of July 28, 1981 (46 FR 38536) to August 18, 1981.

## II. Comments Submitted on The Proposal

The agency received 763 comments on the proposal. Comments were received from 17 State boards of pharmacy or pharmaceutical associations, 14 State medical associations, 4 State osteopathic associations, 1 local osteopathic association, 3 State dental associations, 2 State academies of family physicians, 13 county medical associations, and 7 national associations including the American Medical Association and the American Pharmaceutical Association. Lilly submitted comments on January 31, 1981. The remaining comments were from individual practitioners.

1. The American Pharmaceutical Association took no position on the substantive issues related to the proposal. Rather, the association asserted that a final rule revoking provisions for certification taking effect on the date of publication, as proposed, would lead to substantial confusion on the part of health care practitioners, with resulting disruption of patient care. The association requested that the final rule not take effect until after a reasonable period of time to establish alternative drug therapy for patients under treatment.

The provisions for certification of the estolate tablets and capsules are not being revoked. Thus, it is not necessary to consider the impact of the effective date of a final rule revoking certification provisions.

2. Many of the comments, from associations as well as individuals, requested that the agency submit the issue of the safety of the estolate to an advisory committee before making a final decision.

The issues involved in the determination of the risks and benefits of the estolate were submitted to an advisory committee for independent scientific review. The Committee's conclusions are set forth below.

3. The majority of the comments from practitioners objected to the Bureau's propoasl and requested that the estolate remain on the market. The objections were based on years of personal experience with the estolate with little evidence of hepatic reaction. The agency received three comments supporting its proposal. These comments were also based on the personal experience of the commenters.

4. In its comments Lilly claimed that the proposal was based on an erroneous legal premise—that of relative efficacy. The firm charged that although the proposal was ostensibly based on a conclusion that the estolate is not safe, in actuality it is based only on comparisons of the estolate's bioavailability (essentially an effectiveness determination) with that of other erythromycins. According to Lilly, actions against drugs based on assertions that other drugs are more effective are prohibited by the Federal Food, Drug, and Cosmetic Act.

Lilly misconstrues the agency's action and the nature of a safety determination when it charges that it is engaging in a determination of relative efficacy. The determination of the safety of a drug often includes a determination of its risks and benefits. To the extent that benefits involve effectiveness, safety determinations unavoidably involve some consideration of effectiveness. Certain side effects may be judged to be acceptable when balanced against the potential benefits of a drug. Further, if the drug under consideration is one of a class of drugs indicated for the same conditions, the safety of the one drug cannot be determined without consideration of the safety of the others. A somewhat greater incidence of side effects may be tolerated in the drug under consideration, as compared the class as a whole, if those side effects are sufficiently offset by greater benefits, when compared to the class as a whole. This balancing test is improperly characterized as relative efficacy.

In this case, then, the safety of the estolate was at issue. A somewhat greater incidence of side effects (safety considerations) had been tolerated in the estolate because they were thought to be offset by greater benefits when compared to other drugs in the class. When the agency tentatively determined that the benefits were no greater than the class, it was the estolate's greater potential for harm that resulted in the proposed revocation.

## III. Summary of Data Presented

At the hearing, data were presented by the Bureau of Drugs, Lilly, HRG, and 10 individuals. The most significant data presented by HRG (in its petition and at the hearing), the Bureau, Lilly, and interested persons are summarized below. Data presented by individuals are specifically described only when they differ significantly from the data presented by the Bureau, Lilly, or HRG.

### HRG Petition and Presentation of Data

#### *A. Incidence of Hepatic Reactions*

HRG asserted that the risks of hepatotoxicity from erythromycin estolate outweigh its therapeutic benefits. It requested that all dosage forms be removed from the market. It cited the Bureau's figures from voluntary adverse drug reaction (ADR) reports indicating that hepatic reactions (hepatitis, jaundice, cholestatic jaundice, abnormal liver function) occur 45 times more frequently with the estolate than with generic erythromycin, 16 times

more frequently than with Erythrocin (film-coated erythromycin base, manufactured by Abbott Laboratories), and 6.9 times more frequently than with erythromycin ethyl succinate. Thus, patients who use the estolate are roughly 20 times more likely to suffer drug-associated hepatotoxicity than if they were to use another form of erythromycin. At the hearing HRG asserted that even if only one in a thousand people taking the estolate has a hepatic reaction, it would amount to over 3,500 cases a year in the United States (3.8 million prescriptions were filled in 1980).

The petitioner also described a study undertaken in 1977 said to demonstrate the toxicity of erythromycin estolate (Ref. 1). Of a group of pregnant women receiving 250 milligrams (mg) of the estolate for three weeks or longer, 14.4 percent developed subclinical, reversible hepatic toxicity. Of the 97 patients who received erythromycin stearate, only 3 percent developed abnormal SGOT levels (a test measuring hepatic dysfunction). The investigators stated that there was no convincing evidence that erythromycin estolate offered any clinical advantage.

*B. Description and Effects of Hepatotoxicity*

The petitioner cited the 1977 AMA Council of Drugs *Drug Evaluation Book* (3rd ed.) and Goodman and Gilman, *The Pharmacologic Basis of Therapeutics*, which state that hepatotoxicity is associated only with the estolate. The petitioner also quoted two patients who had suffered an hepatic reaction to the estolate. "These reactions are not mild; I was incapacitated for five weeks because of the liver reaction." Another said, "I became more ill than I've ever been in my entire life."

At the hearing Dr. Fenton Schaffner, Chief of the Division of Liver Disease in the Department of Medicine at Mount Sinai School of Medicine, appeared on behalf of HRG. Dr. Schaffner stated that even though there is no evidence of resulting chronic liver disease and only a few persons are affected each year, there is a significant amount of time lost and cost to the community. For these reasons, he supported removing the drug from the market.

Petitioner contended that hepatic reactions to the estolate, though reversible, are not benign. It cited five cases in the literature where unnecessary surgery resulted from a reaction to the estolate and contended that more cases of unnecessary surgery have, no doubt, occurred than are ever reported (Refs. 2 through 6).

*C. Bioavailability and Clinical Effectiveness*

HRG contended that the higher blood levels obtained with the estolate (free base and estolate levels combined) do not translate into therapeutic superiority. The petitioner cited several studies demonstrating that the estolate is hydrolyzed to free base only to the extent of 20 to 25 percent (Refs. 7, 8, and 9). In addition, HRG contended that the estolate is protein-bound to a higher degree than other erythromycins and, therefore, less likely to be of therapeutic benefit. By comparison, in one study the percent of nonprotein-bound and, therefore, available, drug was seven times greater with the base than with the estolate (Ref. 10). Another investigator found that the percent of free drug was approximately four times greater with administration of the base than with the estolate (Ref. 11).

HRG also contended that no substantial differences have been found in studies comparing the clinical effectiveness of the different erythromycins in the treatment of variety of infections. In 1973 the Commissioner concluded that the estolate was more effective than the base because 30 grams (g) of base were no more effective than 20 g of the estolate in treating primary syphilis. HRG noted, however, that these were not studies of clinical effectiveness, but rather of the 12 month re-treatment rate. The investigators found that the patients given the base had a re-treatment rate of 9.9 percent (Ref. 71), while the patients given estolate had a 14.8 percent re-treatment rate (Ref. 12).

Another study demonstrated that 20 mg/lb of the ethyl succinate was as effective as 7.5 mg/lb of the estolate in treating streptococcal sore throats (Ref. 13). A study comparing the effectiveness of the estolate, the ethyl succinate, and the stearate in 305 patients reported, "The microbiologic failure rates and recurrence rates in patients with Group A beta-hemolytic streptococcal infections of the upper respiratory tract did not differ significantly among three forms of erythromycin . . . ." (Ref. 14) A 1975 study of gonorrhea showed recurrences in 24 percent of the patients treated with the estolate and 23 percent of the patients treated with the base (Ref. 8). The final study presented by HRG was conducted in Australia and purported to show a lower rate of recurrence of strep throat due to estolate suspension (Ref. 15). However, the study was found by the Australian Drug Evaluation Committee not to show any "statistically significant or clinically important" differences between the estolate and stearate suspensions.

HRG asserted that there is no convincing evidence substantiating the claim that the estolate is better tolerated because fewer gastrointestinal side effects occur with it than with other erythromycins. One study compared equal doses of the estolate and the base (Ref. 8). Gastrointestinal side effects were common with both forms, though they were somewhat more common with the base.

Another study obtained opposite results in the comparison of the estolate, the ethyl succinate, and the stearate (Ref. 14). Most adverse reactions occurred in the patients who took the estolate. A third study found no major gastrointestinal adverse effects with either the estolate or the ethyl succinate in 182 patients (Ref. 16).

*D. Pediatric Dosage Forms*

HRG requested that all dosage forms of erythromycin estolate be removed from the market. It included the pediatric dosage forms, asserting that the amount of drug-induced liver damage in children is not insignificant. Petitioner suggested, in addition, that liver disease in children may be reported less frequently than in adults because the disease may be less frequently accompanied by jaundice in children than in adults. Thus, many children who actually suffer liver damage from the estolate may not come to medical attention.

HRG suggested that a further problem with pediatric use of the estolate is the possibility of widespread sensitization. As the children who have been treated with the drug grow to adulthood, subsequent doses could initiate a much higher percentage of toxic reactions than have occurred in today's adults, few of whom were given the drug as children.

HRG noted that the estolate has already been removed from the market in several other countries: in Australia in 1973, in Sweden in 1974, in Denmark in 1975, and in the Netherlands in 1976. No sales have been reported in Austria since February 1980.

In light of these data, HRG concluded that erythromycin estolate is a dangerous and completely unnecessary drug that has been marketed much to long already. They urged the agency to remove all dosage forms as quickly as possible.

**Bureau of Drugs' and Lilly's Presentation of Data**

Data supporting the Bureau's proposal to discontinue certification of erythromycin estolate are summarized

below. Data submitted by Lilly challenging the proposal are also summarized below. The summary includes data submitted by Lilly on October 25, 1979, to the FDA Advisory Committee on Anti-Infective Drugs, on January 18, 1980 at the informal conference, on January 31, 1980, in response to the December 14, 1979 proposed rule, and on March 30, 1981, for submission to the Committee and discussion at public hearing in April 1981.

*A. Adverse Reactions*

Information on the estimates of rates of occurrence of hepatic reactions caused by the various erythromycins was derived from three primary sources: the agency's spontaneous, nationwide adverse drug reaction (ADR) reporting system, a retrospective study of patient records at the Kaiser-Permanente Medical Care Program in Oakland, California, and a review of Medicaid claims records of the States of Michigan and Texas.

Manufacturers are required under 21 CFR 310.301 to submit reports of adverse reactions to the agency's ADR reporting system. Reports from manufacturers are augmented by direct reports from the medical community, the medical literature, contract studies, and foreign data. The reports are evaluated with respect to causality and placed into three general categories: new serious, known serious, and not serious. All reports are placed in a computer file where they can be used to tabulate events thought to be drug-associated and to develop demographic profiles of an effect on the population (Ref. 17).

The study of patient records at the Kaiser-Permanente Medical Care Program (a health maintenance organization) in Oakland, California (K-P study) was commissioned by Lilly in response to the December 4, 1979 proposal (Ref. 18). That study was completed on February 6, 1981. In the study, trained medical record analysts reviewed the records of outpatients during and following 1,078 courses of estolate therapy and 2,583 courses of non-estolate therapy for any evidence of hepatic reactions. The investigators found one probable case of cholestatic hepatitis due to the estolate, and four possible cases due to non-estolate erythromycin.

The Medicaid studies are reviews of patient records under Medicaid. State records are kept of drugs dispensed and physician diagnoses by date of service (Ref. 19). Lilly carried out a study of the Texas and Michigan Medicaid systems. In Texas, the rates of hepatic-related events were 1.9 per thousand adults exposed to the estolate, and 1.86 per thousand adults exposed to non-estolate erythromycin. In Michigan, rates were 4.3 per thousand for the estolate and 2.97 per thousand for non-estolate.

1. *The ADR Reports.*

a. *Bureau of Drugs' Position.* The Bureau made no assertions about the absolute prevalence of the hepatic reactions caused by the estolate and other erythromycins. It did contend, however, that relative prevalence may be estimated from ADR reports because the reporting reflects the actual occurrence of reactions, and on this basis found that relatively more hepatic reactions are caused by the estolate than by other erythromycins.

To estimate the differences in rates of adverse reactions between the estolate and other erythromycins, the Bureau combined ADR data with data on the market share of the drugs. These data were obtained from IMS America's National Prescription Audit and the National Disease and Therapeutic Index. The agency studied the years 1974 (the first year for which market share data were collected) to 1979 (the last year for which market share data were available).

In the 1974–1979 period the Bureau received 315 ADR reports for all salts and esters of erythromycin. If hepatoxicity were equal for estolate and non-estolate erythromycins, then the distribution of ADR reports should follow the market share. An observed/expected ratio can thereby be developed.

The Bureau found that in adults and older children (over 9 years) the average observed/expected ratio for the estolate was 5.2; that is, hepatic reactions were reported 5.2 times more frequently than would be expected based on the market share. Conversely, the average observed/expected ratio in adults for non-estolate erythromycins was 0.19. The difference in these ratios is approximately 27-fold.

In children, (under 9 years) the observed/expected ratio for the estolate was 2.8, while for other erythromycins the ratio was 0.13, a 22-fold difference. The Bureau noted that, because of the very small number of adverse reactions reported for children, these estimates are necessarily imprecise.

The Bureau acknowledged possible weaknesses in this type of data. A chronic problem is the low reporting rate. However, because of the large U.S. population, even rare events are reported a significant number of times over a period of years. Another problem is the variable quality of the data. In the past few years, however, the Bureau has been able to define the kind of information required to make inferences from these data.

The Bureau also acknowledged that the most difficult problem with ADR reports is bias. ADR reports may be used to estimate relative frequency of adverse reactions when there is no major association of an effect with one type of drug in a particular group, there is no major intrinsic bias for reporting on one demographic group as opposed to another, and there in no external biasing factor that would stimulate detection and reporting (e.g., a literature report suggesting the possibility of a previously unsuspected association—the "bandwagon" effect).

A characteristic of this latter bias is that it is not thought to be consistent over time. Therefore, the Bureau argued that if the proportion of reports attributed to the estolate were consistent over a period of years, it can be inferred that the reports reflect actual occurrences and are not due to some sort of bias. The absolute number of reports of hepatic reactions to any erythromycin between 1974 and 1979 was variable, from a low of seven reports in 1979 to a high of 72 reports in 1976. It is noteworthy, however, that the estolate observed/expected ratio (for children and adults, combined) is consistently in the range of three to four times that expected. This is in contrast to the non-estolate erythromycins, which have an observed/expected ratio consistently under unity, ranging from 0.07 in 1974 to 0.67 in 1979.

As a check on the system, the Bureau analyzed the data over time, across demographic characteristics other than the child/adult distinction. For example, in the estolate, the average sex-related observed/expected ratio for males was 0.7; the range is from a high of 1.1 in 1978 to a low of 0.5 in 1975. The average estolate observed/expected ratio for females is 1.3, ranging from a high of 2.0 in 1979 to a low of 1.0 in 1978. These figures are consistent with the hypothesis that women are somewhat more susceptible to hepatic reactions than men, but the important characteristic is the consistency of the figures over time. If the distribution between men and women were very inconsistent from year to year, it could be inferred that some factor other than actual occurrences was stimulating reports.

Similarly, the Bureau examined reports of rashes over time associated with the erythromycins as an additional check on the system. The Bureau found, in children and adults, that the distribution of reports for estolate versus non-estolate tended to

approximate market share year by year. This consistent finding suggests that there was no systematic relative over-reporting of non-hepatic adverse effects associated with erythromycin estolate.

The Bureau discussed briefly ADR data available from foreign countries. The ADR reports from Sweden and Japan corroborated the Bureau's findings: the observed/expected ratios relative to market share for the estolate were 3.7 and 1.7, respectively; and for the non-estolate erythromycins the ratios obtained in both countries were less than one.

b. *Lilly's Position.* Lilly challenged the Bureau's reliance on ADR data, stating that the quality of this information is inferior to data from the K–P and Medicaid studies. The firm stated that ADR data cannot be used to determine the relative frequency of adverse effects, and ought to serve only as warning signals about problems that should be studied by other means. The conclusions drawn from the ADA reporting system may be inaccurate as there was no assurance of an objective decision of "what is a case." Incomplete reports make it difficult to assure a cause-and-effect relationship between a drug and the adverse effect.

Lilly's most significant objection to the use of voluntary ADR reports data was based on the possibility that estolate reactions are reported more frequently than reactions from other erythromycins, in essence, that the reporting is biased. The labeling for the estolate has included information on adverse liver effects since 1961, and two "Dear Doctor" letters concerning the estolate's hepatic effects have been sent to all physicians. The warning was placed in a box in 1974, and an FDA *Drug Bulletin* reiterated the warning. No warnings at all were required for the non-estolate erythromycins until January 1979, however, and these are not boxed warnings. Lilly stated that to assert that these warnings had no effect would be to claim that the entire labeling/warning system is ineffectual.

Lilly stated that just as the number of adverse reactions for the estolate increased after the boxed warning was required in 1973, the number of reactions reported for all erythromycins increased in 1979 and 1980. Three adverse reactions to estolate and four to non-estolate were reported in 1979, and 42 to estolate and 43 to non-estolate were reported in 1980.

Dr. Marcus Reidenberg, Professor of Pharmacology and Medicine, Cornell University Medical College, an individual who spoke at the hearing, noted that any bias against the estolate that is present in the United States would also be present in foreign countries. He also noted that some manufacturers may ascertain a greater fraction of adverse reactions to their products than others. This "ascertainment bias," combined with mandatory reporting by manufacturers, could produce distortions in the data. He suggested the possibility of excluding manufacturers' reports and comparing only the reports of practitioners.

2. *The K–P study.*

a. *Bureau of Drugs' Position.* The Bureau contended that the K–P study, though elegantly conducted, generated insufficient data to allow inference as to the differences in incidence of hepatic reactions due to the various erythromycins. In the study, the investigators reviewed the records of 899 persons who had been given 1,078 courses of estolate treatment and 1,242 patients who had received 2,583 courses of the base, stearate, or ethyl succinate. The investigators found one "probable" estolate-related hepatic reaction and four "possible" non-estolate-related reactions. The Bureau notice the investigators' conclusion that these findings do not allow inference because the adverse effect is so infrequent (estimated to be less than 1 in 500 to 1 in 1,000) that the likelihood of discovering the reaction is low in such a small population.

b. *Lilly's Position.* Lilly contended that many of the problems inherent in data derived from the voluntary ADR reports are absent in data from the K–P study. Lilly stated that the strength of the K–P study lies in the qualifications and experience of the investigators, the use of quality control and standardized procedures, and the accuracy and completeness of the exposure and outcome data. The population at risk was ascertainable—all patients who took either form of erythromycin and belonged to the plan. Therefore, the adequacy of the sample size to find certain differences in treatment may be determined. Lilly believed that the K–P study was large enough to find a difference between treatments if the true difference is 25-fold—that is, if the difference is one adverse reaction per thousand patients (for non-estolate), as compared to 25 adverse reactions per thousand patients (for the estolate). Lilly conceded, however, that the K–P study might not be large enough to detect the differences under consideration in this case—that is, one adverse reaction per thousand patients (for the estolate), compared to 0.04 adverse reaction per thousand patients (for the non-estolate), also a 25-fold difference.

Dr. Reidenberg reviewed his calculation that, assuming a baseline prevalence of one adverse reaction per thousand, a study that could reliably detect a doubling of this prevalence would require the review of 18,000 non-estolate cases and 18,000 estolate cases. He questioned whether the information gained would be worth the cost of such a study.

The firm concluded its discussion of the K–P study by quoting the investigators as saying, "Our study group was too small for us to be able to demonstrate with statistical significance that the cholestatic hepatitis occurred at a greater rate among users of erythromycin estolate than users of the non-estolate forms. Neither can it be concluded from these data that there were no differences."

3. *The Medicaid Studies.*

a. *Bureau of Drugs' Position.* The Bureau stated that the review of Medicaid records is a promising tool for post-market surveillance because of the large number of patients involved, but noted that use of this type of study is still in its infancy. Because of differences in reporting practices, services covered, and refills allowed, it is difficult to compare results among States.

The Bureau found the results of two Medicaid studies to be conflicting with respect to certain age groups. For example, in Texas, hepatic reactions in children under 11, for the estolate and the non-estolate, accounted for 36 percent of all reactions (children and adults). In Michigan, children under 11 accounted for only 8.6 percent of all hepatic reactions. This suggests that the States have different methods of recording diagnoses, that a certain portion of the pediatric population is being missed, or that there is some difference in the tabulation of data between the two States. The Bureau stated that without more information it would be difficult to draw sound conclusions and, therefore, cautioned the Committee against relying too heavily on these data.

b. *Lilly's Position.* Lilly contended that the population at risk in the Medicaid studies is the patients who received either form of erythromycin in the studied States. Lilly asserted that the studies were of sufficient size to demonstrate a one-and-one-half to twofold ratio of risk with high probability. Lilly concluded that the two Medicaid studies are not inconsistent with each other in that both studies indicate similar incidence of hepatic reactions for estolate and non-estolate erythromycins.

4. *Clinical Trials of Hepatic Reactions.*

a. *Bureau of Drugs' Position.* The Bureau presented several prospective clinical trials suggesting that a higher frequency of hepatic dysfunction is associated with the estolate than with other erythromycins. A brief description of the major clinical trials presented follows.

(1) Patients with chronic pustular dermatitis were treated with erythromycin estolate in two series (Ref. 20). The first series included 80 patients; an additional 13 patients were treated in the second series. After 14 to 21 days of therapy, abnormal liver function tests were obtained in 12 percent of the patients in the first series and in 38 percent of the patients in the second series.

(2) The estolate hepatotoxity described in the preceding paragraph, was compared to the hepatotoxicity noted in one patient out of 18 (5 percent) with the stearate (Ref. 21). The investigator also reported that one patient with a history of an hepatic reaction from the estolate had no hepatic dysfunction when treated with the stearate.

(3) Women in the second half of pregnancy received the estolate, clindamycin hydrochloride, or placebo for the treatment of genital mycoplasmal infections (Ref. 1). All pretreatment SGOT levels were normal. Of the 97 women treated with clindamycin hydrochloride, 4 (4.1 percent) developed abnormal SGOT levels. Of the 97 women treated with the estolate, 14 (14.4 percent) developed abnormal SGOT levels. Of the 104 women treated with placebo, 3 (2.9 percent) abnormal SGOT levels. As soon as it was noted that women on the estolate developed a higher rate of abnormal SGOT levels than those taking clindamycin hydrochloride or placebo, incoming patients were given the stearate instead. Of the 97 patients treated with the stearate, 3 (3 percent) developed abnormal SGOT levels.

(4) of 100 patients treated with the estolate for 10 days for acute maxillary sinusitis, 1 patient developed cholestatic hepatitis (Ref. 63).

b. *Lilly's Position.* Lilly reported on six prospective clinical trials investigating hepatic reactins due to the estolate.

(1) No estolate hepatotoxicity was seen in a study of 37 patients. All were given the estolate (Ref. 25).

(2) Twenty-five patients with urinary tract infections were treated with the estolate for two weeks (Ref. 26). The authors report that "no serious toxicity was encountered."

(3) Seventy patients with purulent exacerbations of chronic bronchitis were treated with the estolate for two weeks (Ref. 27). No hepatotoxicity was noted.

(4) There were no liver function test abnormalities in a group of 21 premature infants given the estolate (Ref. 28).

(5) In a comparison of the estolate and penicillin in children, there were no statistical differences between the two groups in elevations of SGOT and bilirubin (Ref. 29).

(6) In an ongoing study of the estolate suspension, ethyl succinate suspension, and penicillin liquid in children with pneumonia, there has been no evidence of hepatotoxicity (Ref. 30).

Lilly reviewed four prospective studies reporting hepatic dysfunction in patients taking the base, stearate, ethyl succinate, or estolate.

(7) Twenty-one patients with cystic fibrosis participated in this study designed to evaluate the relationship of erythromycin prophylaxis and SGOT levels in chronically ill patients (Ref. 31). The authors concluded, "There is no demonstrable effect of erythromycin stearate or erythromycin ethyl succinate upon the SGOT level."

(8) In this study, the SGOT levels of patients receiving the base or the estolate in the treatment of gonococcal urethritis were observed (Ref. 8). The authors report that "abnormal SGOT levels were equally common among patients receiving erythromycin base and the estolate before, during, and after treatment."

(9) In a study of pregnant women given the estolate, the stearate, or placebo, 14.4 percent of the estolate group completing three weeks or more of therapy developed abnormal SGOT levels (Ref. 1; reviewed by the Bureau in paragraph 4.a.(3) above). When the high proportion of abnormal SGOT levels with the estolate was noticed, further incoming patients were given the stearate. Of these patients, 3 percent developed abnormal SGOT levels. Of the patients who received placebo, 2.9 percent developed abnormal SGOT levels.

(10) Patients with chronic pustular dermatitis were treated with the stearate or the estolate (Ref. 21; reviewed by the Bureau in paragraph 4.a. (2) above). Of the first group of estolate patients treated, 12 percent developed hepatotoxicity. Of the second group of estolate patients, 38 percent developed hepatotoxicity. Of the stearate patients, 5 percent developed hepatotoxicity.

Lilly also presented six recently published papers, each reporting one case of hepatic dysfunction due to the ethyl succinate (Refs. 32 through 37).

5. *Other Adverse Reactions.*

a. *Bureau of Drugs' Position.* The Bureau reviewed data on adverse reactions other than those involving the liver obtained from the spontaneous reporting systems of Sweden and the United States. The Bureau found the data to be inconsistent, and no clear conclusions were drawn.

The Bureau studied ADR reports of both gastrointestinal and rash hypersensitivity reactions. These reports of gastrointestinal effects were compared to market share in the same way as reports of hepatic reactions. The Bureau found that the rate of estolate reports in children was 6.7 times greater than that in the non-estolate; in adults, the rate for the estolate was 4.4 times greater than that for the non-estolate. The Bureau noted that some of the gastrointestinal side effects actually may have been subclinical hepatic reactions.

For rash and related effects, the Bureau found that the distribution of reports for the estolate versus the non-estolate tend to approximate the market share in children and adults.

The Bureau presented data from clinical trials which corroborated the inconclusiveness of the ADR reports in regard to gastrointestinal side effects.

(1) The estolate and the base were used in the treatment of gonococcal urethritis (Ref. 8). Of the patients in the base group, 73 percent reported gastrointestinal side effects. Of the patients in the estolate group, 57 percent reported gastrointestinal side effects. The number of patients with vomiting, pain, or moderately severe nausea or diarrhea was 30 percent in the base group and 13 percent in the estolate group.

(2) The base was used in 17 women in the treatment of *Haemophilus vaginalis* (Ref. 22). Therapy was discontinued in four patients due to nausea, diarrhea, and abdominal cramps. Three other patients developed nausea and/or diarrhea, but continued therapy.

(3) Propionyl erythromycin (a closely related forerunner of erythromycin estolate) was given to 134 children and adults who were contacts and carriers of staphylococci and streptococci (Ref. 23). The drug had to be discontinued in six children because of severe vomiting, abdominal cramps, and severe nausea.

(4) In a comparison of the ethyl succinate, stearate, and estolate in streptococcal infections, 156 patients were given the estolate, 102 were given the ethyl succinate, and 47 were given the stearate (Ref. 14). Of eight patients

developing gastrointestinal side effects, seven were in the estolate group. One adult taking the estolate developed loose stools and pruritus ani. Therapy was discontinued in two children taking the estolate because of nausea and abdominal cramps. Another four children treated with the estolate reported nausea, vomiting, abdominal cramps, and diarrhea, but continued therapy. One child treated with the ethyl succinate developed a moderate skin rash and vomiting, but therapy was not stopped.

(b.) *Lilly's Position.* Lilly stated that gastrointestinal side effects are dose-related and less frequent for the estolate than the non-estolate. Because of these side effects, it is usually not possible to increase the dosages of enteric-coated base, stearate, or ethyl succinate to achieve blood and tissue concentrations comparable to those obtained with the estolate.

The firm reviewed four clinical trials investigating gastrointestinal side effects.

(1) Of patients treated with the estolate, 13 percent reported severe to moderately severe effects, while 30 percent of patients treated with non-estolate reported side effects, two stopping treatment (Ref. 8; reviewed by the Bureau in paragraph 5.a.(1) above).

(2) In a study using erythromycin base, 4 of 17 patients stopped treatment because of nausea, abdominal cramping, or diarrhea (Ref. 22; reviewed by the Bureau in paragraph 5.a.(2) above). Three others experienced these side effects but continued treatment.

(3) In a comparative study of they estolate, stearate, and penicillin in treating disseminated gonococcal infections, three of five stearate-treated patients developed nausea and vomiting, therapy was discontinued in one. One of nine estolate-treated patients experienced nausea but continued treatment, while none of the nine penicillin-treated patients vomited or discontinued therapy (Ref. 38).

(4) In a study of 269 patients given the stearate, 33 percent of the patients experienced gastrointestinal disturbance (Ref. 39). Five percent of the patients discontinued treatment because of vomiting, abdominal pain, or diarrhea.

Studies in dogs indicate that erythromycin has a stimulating effect on the smooth muscle and the motility of the intestine (Ref. 40). The firm suggested that this effect might be the cause of the reported nausea, vomiting, and diarrhea. The base, stearate, and ethyl succinate being absorbed to a lesser extent than the estolate may result in higher residual erythromycin concentrations in the bowel lumen, thus causing more gastrointestinal side effects.

Lilly concluded that the lower rate of gastronintestinal effects associated with the estolate may be of clinical significance because physicians often advise that the drugs be taken with food to decrease gastronintestinal disturbances. However, food can interfere with the absorption of non-estolate erythromycins.

6. *In Vitro Data.* Dr. Hyman Zimmerman, Professor of Medicine at George Washington University, appeared at the hearing on behalf of the Bureau. He discussed the significance of biochemical abnormalities, stating that drugs that cause overt jaundice are likely to cause a higher incidence of abnormalities than those that are not associated with overt jaundice (Ref. 24). He referred to a number of in vitro studies conducted with chlorpromazine, which has about a one percent incidence of jaundice, and promazine, which has a very negligible reported rate of jaundice. Observations in Chang liver cells, rat hepatocytes, rabbit liver slices, and perfused liver indicate that chlorpromazine caused significantly more injury. This is consistent with the hypothesis that drugs that produce injury by hypersensitivity can produce injury in in vitro models.

When the estolate was compared with the base in a similar manner, Dr. Zimmerman stated that the estolate, but not the base, led to injury in Chang liver cells in suspension or culture, to suspensions of rat hepatocytes and the isolated, perfused rat liver. Dr. Zimmerman noted that translation of in vitro observations to in vivo phenomena must be made with caution, but in light of the clinical data with which the in vitro observations are consistent, these data are convincing.

*B. Bioavailability*

A summary of the bioavailability data presented by Lilly and the Bureau follows.

1. *Blood Levels of Free Base.* Erythromycin estolate appears in the blood as the total propionyl ester and, through hydrolysis, as free base. FDA's Anti-infective Agents Advisory Committee concluded in 1973 that the estolate is likely to be more effective than other erythromycins because of higher blood levels. However, the data reviewed by the Committee at that time did not distinguish between levels of free base and the levels of propionyl ester obtained. The estolate produces blood levels of total erthromycin three to four times higher than those obtained after administration of the base or stearate.

The Bureau's assertion that the estolate is not more bioavailable than other erythromycins is based on the results of bioavailability studies conducted by the University of Texas in Austin. These studies used as assay method that quantitatively differentiated the free base in presence of the ester.

a. *Bureau of Drug's Position.* The Bureau contended that erythromycin estolate does not possess significant antibacterial activity until it has been hydrolyzed to the base. Therefore, the Bureau asserted that a comparison of the levels of free base obtained with the different erythromycins is more meaningful than a comparison of total erythromycin levels. The Bureau discussed the results of 11 recent studies which compared the bioavailability (as indicated by blood levels) of erythromycin estolate with that of another erythromycin. Bioavailability was determined by newly developed methodology which permitted differentiation between the levels of free base and the particular salt (estolate, stearate, or ethyl succianate).

The Bureau argued that all but one of the studies indicate that, in terms of free base, the estolate is not more bioavailable than other erythromycins: the estolate was equally or less bioavailable. (Although there may be exceptions, it is generally true that if one drug in oral dosage form is 80 to 120 percent as bioavailable as the reference drug in oral dosage form, the two drugs are considered bioequivalent.) A brief description of those studies follows. The bioavailability values given are in terms of free base.

(1) The University of Texas Study—a comparison of estolate and stearate, single-dose, fasting (Ref. 41). The estolate was 45 percent as bioavailable as the stearate. The mean peak concentration for the estolate was 25 percent that obtained with stearate.

(2) The University of Texas Study—a comparison of estolate capsules, enteric-coated base tablets, and stearate tablets, multiple-dose, fasting (Ref. 41). The study employed 24 volunteers in a crossover design. A total of five doses was given every six hours.

After the first dose, the estolate was 36 percent as bioavailable as the base, and 65 percent as bioavailable as the stearate. After the fifth dose, however, there was no difference between the drugs—the estolate was 88 percent as bioavailable as the base and 135 percent as bioavailable as the stearate. Cumulative values (after doses 1, 2, and 5) indicate that the estolate is 66 percent as bioavailable as the base and 96

percent as bioavailable as the stearate. Thus, the estolate is not more bioavailable than the base or stearate.

(3) A comparison of estolate capsules and stearate tablets, single-dose, fasting (Ref. 42). Blood levels were monitored for 12 hours after dose administration. The estolate was 22 percent as bioavailable as the stearate. The mean peak concentration of free base for the estolate was 24 percent that of the stearate.

(4) A comparison of estolate capsules and stearate, single-dose, nonfasting (Ref. 42). The presence of food reduced the bioavailability of the stearate and increased that of the estolate. However, the estolate was still only 89 percent as bioavailable as the stearate. The mean peak concentration for the estolate was only 64 percent that of the stearate.

(5) A comparison of estolate capsules and stearate tablets, multiple-dose, fasting (Ref. 42). A total of five doses was given and blood samples were drawn periodically after the fifth dose for 12 hours. The bioavailability of the estolate was 47 percent that of the stearate. The mean peak concentration was higher for the stearate than for the estolate.

(6) A comparison of estolate capsules and stearate tablets, multiple-dose, nonfasting (Ref. 42). As in the previous study, a total of five doses was given and blood samples were drawn periodically after the fifth dose for 12 hours. The bioavailability of the estolate was found to be 66 percent of the stearate.

(7) A comparison of estolate capsules and enteric-coated base, multiple-dose (Ref. 43). Twelve doses were given to 16 volunteers in a crossover study. A two-hour fast was observed before and after drug administration. Samples were taken until the eighty-fourth hour. The estolate was not shown to be more bioavailable than the base. After the first two doses, the estolate was 90 percent as bioavailable as the base. After doses 9 through 12, the mean cumulative bioavailability of the estolate was 99 percent of the base. After the first and ninth doses the differences in the mean peak concentration was statistically significant in favor of the base. After all other doses, the differences in mean peak concentration were not significant.

(8) A comparison of estolate capsules and enteric-coated base tablets, nonfasting, multiple doses (Ref. 44). A total of 12 doses was given during 72 hours. Blood levels were monitored after doses 1, 2, 9, 10, 11, and 12. The estolate was not shown to be more bioavailable than the base. After the first two doses the bioavailability of the estolate was 109 percent that of the base. After doses 9 through 12, the mean cumulative bioavailability of the estolate was 85 percent that of the base. The mean peak concentration for the base was higher at each measurement than that of the estolate, but was not statistically significant.

(9) A comparison of estolate capsules and ethyl succinate tablets, multiple dose, nonfasting (Ref. 45). This was a two-way crossover study; five doses of each drug were given every six hours. Blood levels were measured at specified intervals for 36 hours. The mean peak concentration after each dose was higher for the ethyl succinate than for the estolate. After the first dose the ethyl succinate was 11 percent more bioavailable than the estolate. After the fifth dose, the estolate was 25 percent more bioavailable than the ethyl succinate. However, the hydrolysis data indicate that after the fifth dose the ethyl succinate was 75 percent hydrolyzed, rather than 50 to 60 percent. On the basis of 75 percent hydrolysis to base, the bioavailability of the estolate was only 6 percent higher than that of the ethyl succinate. The cumulative bioavailability of free base after doses 1, 2, 3, and 5 was 92 percent for the ethyl succinate in comparison with the estolate.

(10) A comparison of estolate capsules and ethyl succinate tablets, multiple dose (Ref. 46). A total of three doses of each drug was given. The first and second doses were given under fasting conditions; the third dose was given 20 to 30 minutes after breakfast. The cumulative bioavailability of the ethyl succinate was 91 percent that of the estolate. Under the nonfasting state of the third dose, the ethyl succinate was 93 percent as bioavailable as the estolate.

(11) A comparison of the estolate suspension and the ethyl succinate suspension, multiple dose, nonfasting (Ref. 47). This was a two-way crossover study using 25 volunteers. Each drug was given every six hours for a total of nine doses. In this study significantly superior blood levels were obtained from the estolate. The bioavailability of the estolate was 296 percent that of the ethyl succinate after the first dose. After the fifth and ninth doses it was 427 percent and 496 percent respectively. The mean peak concentration after the first, fifth, and ninth doses show the same trend.

The Bureau pointed out that 400 mg of the estolate and the ethyl succinate were administered, but that the normal dose of the estolate is only 250 mg while that of ethyl succinate is 400 mg. However, even after normalizing the values of 400 mg dose to 250 mg dose of the estolate, higher blood levels of free base were obtained with the estolate.

b. *Lilly's Position.* Lilly's presentation was aimed at refuting the Bureau's statement in the December 4, 1979 **Federal Register** that "The bioavailability of erythromycin estolate, in terms of free base, is, if anything, poorer than that of other erythromycins tested" and at establishing that the estolate is more reliably absorbed than other erythromycins. Lilly reviewed essentially the same studies presented by the Bureau. The firm's discussion of the studies is described below. The paragraphs referred to are in the Bureau's presentation, above. Unless otherwise noted, bioavailability is in terms of free base.

a. *Blood Levels of Free Base.* (1) Lilly criticized the University of Texas studies (Refs. 55 and 56; described in paragraphs (1) and (2) above as Ref. 41) because they did not include all forms of erythromycin and because they were conducted under fasting conditions. The firm stated that, in practice, erythromycin is often taken with food because the gastrointestinal side effects of all forms are then reduced. In addition, Lilly briefly discussed a clinical trial indicating that the presence or absence of food can greatly influence the bioavailability of erythromycin products (Ref. 57).

In regard to the single-dose University of Texas study, Lilly cautioned, as did the investigator, against drawing conclusions from a single-dose study alone, as it might lead to erroneous conclusions. Lilly also asserted that the variability among subjects was so great that differences in blood levels of free base were not statistically significant.

The firm noted that, in the multiple-dose University of Texas study, both the stearate and the base produced widely variable blood levels of free base between doses, compared with the gradual but steady rise of free base levels obtained with the estolate. In addition, the firm noted that after steady-state conditions were reached, the mean bioavailability for the estolate was greater than that for the stearate, but noted that the investigators concluded that the difference was not statistically significant.

(2) Lilly discussed the multiple-dose study of the estolate capsules with enteric-coated base under nonfasting conditions described in paragraph (7), above (Ref. 43). In that study, patients were administered 12 doses of a drug, one every six hours.

After the first dose on the third day—the ninth dose—the estolate produced

blood levels which were only 73 percent of those of the base. However, over a full day for the four steady-state doses, (doses 9 through 12) the estolate was 99 percent as bioavailable as the base. The firm concluded from this that conclusions drawn from the multiple-dose University of Texas study (in which only five doses were given over the course of the study) would unrealistically favor the base.

(3) In order to determine the relative bioavailability of the estolate under conditions closely related to medical practice, Lilly undertook a study comparing estolate capsules with enteric-coated base in volunteers immediately after meals (Ref. 44; described in paragraph (8), above). As did the Bureau, Lilly concluded that this study demonstrated that the estolate and base are essentially bioequivalent, and noted the large intersubject variability with the base.

Lilly claimed its comparison of this study and the University of Texas studies shows that the variability of blood levels in patients receiving the base increases markedly when it is administered with food. However, with the estolate, blood levels are relatively constant whether or not the drug is taken with food. After the first dose in the Texas study, the percent standard deviation of the serum erythromycin base concentrations was 109 percent (range, 43 to 275 percent) for the base, and 56 percent (range, 38 to 82 percent) for the estolate. Under pseudo-steady-state conditions, this percent standard deviation decreased to 84 percent (range, 44 to 167 percent) for the base, and 36 percent (range, 30 to 47 percent) for the estolate. When the same products were adminstered immediately after meals in the Lilly study, the percent standard deviations of the serum erythromycin based concentration for the first dose of the base was 170 percent (range, 100 to 422 percent) decreasing to 63 percent (range, 35 to 117 percent) under pseudo-steady-state conditions. For the estolate capsule, the percent standard deviation was 69 percent (range, 48 to 83 percent), decreasing under steady state conditions to 40 percent (range, 29 to 51 percent).

(4) Lilly discussed two unpublished studies comparing estolate capsules and ethyl succinate tablets (Ref. 45; described in paragraph (9) and Ref. 46 described in paragraph (10), above). In the first study, patients were given 250-mg capsules of estolate and 400-mg tablets of ethyl succinate. In the second study, patients were given 500 mg of the estolate or 800 mg of the ethyl succinate. In both studies the total erythromycin blood levels for the estolate were two to four times that of the ethyl succinate despite the 60 percent greater dosage of the ethyl succinate. Lilly stated that in the first study the estolate was hydrolyzed to free base to the extent of 23 percent, while the ethyl succinate was hydrolyzed to the extent of 57 percent. In the second study, the blood levels for the estolate were 2.2 times that of the ethyl succinate after the first dose, 3.1 times greater after the second dose, and 2.7 times greater after the third dose. Free base was present in approximately the same proportion.

(5) Lilly presented two studies comparing the estolate oral suspension with the ethyl succinate oral suspension. In the first study (not reviewed by the Bureau) the investigators found that significantly higher concentrations of total erythromycin and the free base were obtained with the estolate than with ethyl succinate when they were administered with food (Ref. 58). Although a greater proportion of the ethyl succinate is hydrolyzed to resulting free base, the free base concentration from the ethyl succinate is only about one-sixth that obtained from the estolate.

The second study of oral suspensions is described in paragraph (11) above (Ref. 47). The firm noted the Bureau's statement that even after normalizing the doses, the levels of free base for estolate were significantly higher than those of the ethyl succinate.

(6) Dr. Charles Ginsburg, Director of Ambulatory Services at the University of Texas, Southwestern Medical School, an individual who appeared at the hearing, reported on several studies he had conducted comparing liquid preparations of the estolate and the ethyl succinate administered with or without milk to children (no citation was given). He emphasized that there are only two liquid preparations of erythromycin available—the estolate and the ethyl succinate. Dr. Ginsburg's data corroborated Lilly's data. The administration of milk did not affect the bioavailability of either drug.

2. *Reliability of Absorption.*

a. *Bureau of Drugs' Position.* The Bureau noted that the intersubject variation in the absorption of the estolate appears to be smaller than that of enteric-coated base. In the multiple-dose, non-fasting study described in paragraph (8) of the Bureau's presentation, above, the coefficient of variation (an indication of intersubject variation) for the base after the first two doses was twice as large as that of the estolate (Ref. 44). After the ninth dose, the coefficient of variation of the base is 15 to 20 percent higher for the base than that of the estolate. Of the 24 patients receiving the base, seven failed to attain measurable blood levels in the first six hours after drug administration. One subject had no measurable blood level for 12 hours following the first dose of the base. All subjects who received the estolate, however, had measurable levels of free base within three hours after the first dose. However, the Bureau stated that there appears to be no clinical advantage to the greater reliability of absorption of the estolate because a patient with an infection so serious as to require immediate blood levels would likely be hospitalized and receiving antibiotics intravenously.

b. *Lilly's Position.* Lilly contended that the estolate is the most reliably and completely absorbed form of erythromycin, with total erythromycin concentrations several times those obtained following administration of other erythromycins. In addition, essentially the same total erythromycin concentrations are obtained when the estolate is administered with or without food and with different volumes of water. Four studies were cited to support these contentions (Refs. 42, 59, 60, and 61).

The absorption of enteric-coated base was said to be highly variable. In a study of fasting subjects administered enteric-coated base every six hours (not reviewed by the Bureau), steady-state blood levels of the drug were generally higher each day after the first and second doses than after the third and fourth doses (Ref. 62). This variability in concentration with time of day was repeatedly observed.

That blood levels obtained with the stearate are variable and influenced by food and fluid was confirmed in the University of Texas study. Lilly quoted the investigators: "Overall, the absorption of erythromycin stearate is markedly decreased when administered shortly after a meal and appears not to be affected if dosing occurs one hour prior to a meal."

3. *Tissue Concentration.*

a. *Bureau of Drugs' Position.* The Bureau reported on three tissue concentration studies: tonsil, aqueous humor, and middle ear exudate (Refs. 48, 49, and 50). Two studies compared the estolate with the ethyl succinate; the aqueous study compared the estolate with the base. In these studies, bioavailability was determined in terms of total erythromycin. The estolate is approximately 20 percent hydrolyzed in vivo, and the ethyl succinate is, on the average, 50 percent hydrolyzed to free

base in vivo. The Bureau, therefore, estimated the levels of free base by dividing the estolate levels by five, and the ethyl succinate levels by two. The Bureau concluded that although the estolate sometimes produced higher tissue levels of free base than other erythromycins, there appeared to be no clinically significant advantage of one erythromycin preparation over another. (See *Clinical Effectiveness* section, below.)

b. *Lilly's Position.* Lilly discussed several tissue concentration studies. Studies of erythromycin estolate concentrations in maxillary sinus exudate and tears were not comparative, and Lilly simply reported the results (Refs. 63, 64, and 65). Lilly also discussed the tonsil tissue, aqueous humor, and middle ear exudate studies presented by the Bureau (Ref. 48 described in Bureau's position above). The firm stated that the higher tonsillar levels for the estolate may have therapeutic implications because in vitro studies show that progressive increases of erythromycin concentrations above the minimum inhibitory concentration for beta-hemolytic streptococci result in an accelerated killing rate.

Dr. Ginsburg reviewed a study in which he found significant differences (in favor of the estolate) between levels of erythromycin obtained from estolate and ethyl succinate liquid preparations in the tears of children (no citation was given). (There were no significant differences in the salivary concentrations between the two drugs.) Dr. Ginsberg suggested that the higher tear levels may be of clinical significance in a diseases of the eye and lung caused by chlamydia in children.

4. *Therapeutic Effect of Propionyl Ester.*

a. *Bureau of Drugs' Position.* The Bureau contended that the propionyl ester has no therapeutic effect other than serving as a reservoir out of which active free base is hydrolyzed.

The Bureau reviewed the results of Lilly's mouse protection studies which compared the effectiveness of intravenously administered propionyl ester and erythromycin base against experimentally induced *Streptococcus pyogenes* infections (Ref. 51). (The drugs were administered intravenously in order to minimize variation due to absorption differences.)

When mice were treated 1 hour post-infection, the median effective dose of the base was 16 mg/kg, while that of the propionyl ester was 24 mg/kg. When treatment was given 2 hours pre-infection, the median effective dose of the base increased to 41 mg/kg, while that of the propionyl ester was 29 mg/kg.

The propionyl ester hydrolyzes into free base at a relatively slow rate (one half-life is 93 minutes). Thus, the Bureau argued that this single dose study is biased in favor of the propionyl ester. In normal treatment of bacterial infections, treatments must be continued for several days or relapse will occur. When the base was given after infection, the protective effect was too short-lived. The greater protection from administration of the propionyl ester was due to the prolonged effect of its continued hydrolysis long after the comparative erythromycin base dosage had been eliminated from the mice's systems.

The Bureau reviewed two in vitro studies which, it claimed, indicate that the propionyl ester is inactive and that any activity in its solutions is proportional to its hydrolysis rate.

(1) Five of the 2' esters of erythromycin were ranked in order of hydrolysis (Ref. 52). The ester with rapid hydrolysis performed with full activity as soon as it was applied to growing cultures. The propionyl ester had a slow onset of bacteriostatic activity coinciding with its slow hydrolysis rate.

This study also evaluated the ability of various erythromycin esters to inhibit radio-labeled erythromycin from binding to ribosomes. (It is through ribosomal binding that erythromycin exerts its bacteriostatic effect by inhibiting protein synthesis.) The propionyl ester was unable to displace significant amounts of the labeled erythromycin from the ribosomes—the amount of binding by the esters was proportional to their hydrolysis rates.

(2) That the antimicrobial effect of the estolate is due to hydrolysis of the propionyl ester to free base was urged by the Bureau to have been demonstrated by a second study comparing bactericidal effects at different pH levels (Ref. 53). There was a very slow and gradual appearance of activity from the propionate solutions at pH unfavorable for hydrolysis (pH 6.0). There was, however, a rapid and complete appearance of anti-bacterial activity at a favorable hydrolytic pH (pH 7.5).

The Bureau contended that there is no direct evidence of hydrolysis taking place after the propionyl ester is absorbed by bacterial cells. Strong indirect evidence, however, points to lack of hydrolysis within cells.

An unpublished study indicates, by use of radioactive tracers, that the propionyl ester is absorbed into bacterial cells to a much greater extent than is erythromycin base (Ref. 54). The Bureau stated that if the ester were hydrolyzed to an active form intracellularly, the ester would show much higher activity than the base in vitro studies. It does not.

Finally, the Bureau cited Lilly's attempts to find bacterial esterases capable of splitting the estolate. The firm was able to find esterases capable of splitting ester complexes other than the propionyl ester of erythromycin. Thus far, the search for enzymes capable of splitting the propionyl erythromycin ester within the bacterial cell has been unsuccessful.

b. *Lilly's Position.* Lilly contended that the propionyl ester has a therapeutic effect in addition to its providing a reservoir from which the base is continously hydrolyzed. It argued that the ester configuration modifies the chemical, physical, and biological characteristics of erythromycin and increases its lipid solubility. This facilitates its penetration into macrophages and tissues. Thus, the ester acts as both a reservoir and a delivery system of erythromycin.

Lilly stated that if a significant amount of the propionyl ester enters the bacterial cell and intracellular hydrolysis occurs, then an antibacterial effect should be observed. Lilly reviewed the studies evaluated by the Bureau indicating that the propionyl ester is accumulated intracellularly to a great extent than the base (Ref. 54). The firm noted that techniques have not yet been developed for determining actual intracellular hydrolytic activity. However, because there has not yet been found a medium in which the propionyl ester is not hydrolyzed to free base, it can only be assumed that the estolate within cells is a source of active free base.

Lilly reviewed studies which indicate that the uptake of antibiotics by alveolar macrophages is related to lipid solubility—the more lipid-soluble drugs being concentrated to a greater extent than the non-lipid-soluble drugs (Refs. 67 and 68). At 1 minute, the concentration of the estolate was 17 times that of the base, at 15 minutes, the difference was six times; and at 1 hour, the ester concentrations were twice that of the base. The firm suggested that this characteristic might be significant in difficult-to-treat infections caused by viable intracellular bacteria such as Legionnaire's disease and *Chlamydia trachomatis.*

Lilly reported on the mouse protection study comparing the effectiveness of intravenously administered propionyl ester and erythromycin base against experimentally induced *Streptococcus*

*pyogenes* infections (Ref. 51; reviewed by the Bureau above).

The median effective dose for the propionyl ester was higher than that for the base. However, chromatographic analysis indicates that the amount of active free base hydrolyzed from the propionyl ester was significantly less than the median effective dose of the base. Thus, Lilly argued that the propionyl ester itself appears to have provided the requisite additional antimicrobial activity. These results were confirmed in a second mouse protection study performed in mice infected with *S. pyogenes* and *S. aureus* (Ref. 69, noted reviewed by the Bureau).

*C. Clinical Effectiveness*

1. *Streptococcal Pharyngitis and Tonsillitis (strep throat).* The recommended children's dose for the ethyl succinate, the stearate, and the base is 30 to 50 mg/kg/day in the treatment of streptococcal pharyngitis. In 1978, the recommended dose for the estolate in the treatment of streptococcal pharyngitis in children was changed from 30 to 50 mg/kg/day to 20 to 50 mg/kg/day based on data submitted by Lilly (Ref. 118).

a. *Bureau of Drugs' Position.* The studies submitted by Lilly to support the labeling change investigated only the estolate. Other studies (described below) indicated that higher doses of the ethyl succinate suspension are as effective as lower doses of the estolate suspension. The difference in dosage amount is not very great and appears to be of little clinical significance as there appear to be no adverse effects (i.e., gastroinstestinal) from higher doses of the ethyl succinate. In addition, there is no difference in effectiveness between low doses of the estolate capsules (23 mg/kg/day) and comparable doses of the stearate tablets (23.1 mg/kg/day) (Ref. 14—described below).

(1) Erythromycin estolate was used successfully in the treatment of children at a dosage of 20 mg/kg/day (Ref. 70). This study made no comparison with other erythromycins.

(2) In a comparison of the estolate and the ethyl succinate in children, eradication rates were similar in both groups (Ref. 16). The dosage of the ethyl succinate was 40 mg/kg/day, while that of the estolate was 20 mg/kg/day. The effectiveness of the ethyl succinate at lower doses was not studied.

(3) This study compared two dosage schedules of the ethyl succinate oral suspension with penicillin in oral suspension (Ref. 13). One regimen of the ethyl succinate was the usually recommended dosage (44 to 50 mg/kg/day) while the other was below the usual recommended dose (27.5 to 33.4 mg/kg/day). There was no significant difference between the results of penicillin and the higher, usually recommended, dose of the ethyl succinate.

The higher dosage of the ethyl succinate was then compared with penicillin and the estolate given below the usual recommended dose (10 to 20 mg/kg/day) and at the usual recommended dose (20 to 50 mg/kg/day). There seemed to be no difference in the effectiveness of the estolate and the ethyl succinate when both were given at the recommended dose. The authors concluded that the dosage of the ethyl succinate should be above 39.5 mg/kg/day, but that the estolate was as effective as penicillin at 16.5 mg/kg/day in patients under 45.4 kg.

(4) This study compared ethyl succinate suspension (51.4 mg/kg/day) and the estolate suspension (31.8 mg/kg/day) (Ref. 14). The cure rate for the ethyl succinate was 97.9 percent, while that of the estolate was 93.3 percent.

In the same study, the investigators compared ethyl succinate chewable tablets (38.7 mg/kg/day) with estolate chewable tablets (38.3 mg/kg/day). The cure rate of the ethyl succinate was 90.9 percent, while that of the estolate was 95.7 percent.

A third comparison was made in the same study, between stearate tablets (23.2 mg/kg/day) and estolate capsules (23.0 mg/kg/day). The cure rate for the stearate was 100 percent; that of the estolate was 95.8 percent.

b. *Lilly's Position.* Lilly reviewed the studies reviewed by the Bureau indicating that the estolate is effective in the eradication of streptococcal microorganisms at 15 to 20 mg/kg/day (Refs. 13, 14, 16, and 70).

Dr. Ginsburg presented preliminary results of an ongoing study comparing the effectiveness of the estolate (15 mg, twice daily) to the ethyl succinate (15 mg, twice daily) in the treatment of strep throat (Ref. 120). The author stated that no study had compared the effectiveness of the ethyl succinate with the effectiveness of the estolate when both were given at the lower dose at which the estolate is effective. It is essential to determine whether the ethyl succinate may also be effective at the lower doses. Of the 100 patients studied so far, 52 were given the estolate with an 11-percent failure rate. Of the 48 patients given the ethyl succinate, there was a 31-percent failure rate.

2. *Primary Syphilis.*

a. *Bureau of Drugs' Position.* No comparative studies of the effectiveness of the estolate and other erythromycine have been conducted. (The only studies have been of re-treatment rates. These studies clearly cannot demonstrate effectiveness.) Thus, the Bureau stated that it cannot be determined whether the estolate is more effective than othe erythromycins.

(1) This study investigated the re-treatment rates of different dosages of erythromycin estolate in the treatment of primary syphilis (Ref. 71). One year after treatment, the re-treatment rate for the 10 g schedule was 35 percent, while that of the 15 to 20 g schedule was 15 percent. Based on this study, the Public Health Service recommends 10 days of orally administered erythromycin in a total dosage of 20 g. The recommendation does not specify a particular form of erythromycin.

(2) This study compared the 12-month re-treatment rates of 20-g schedule of erythromycin base and and 30-g schedule of the base (Ref. 12). A 25-percent re-treatment rate was obtained with a 20-g schedule, while a 9.9-percent re-treatment rate was obtained with the 30-g schedule. The authors concluded that erythromycin base in a total of no less than 30 g for 10 days is an acceptable alternative to penicillin in the treatment of early syphilis.

b. *Lilly's Position.* Lilly submitted no additional studies on the effectiveness of erythromycin on the treatment of primary syphilis.

3. *Haemophilus influenzae Otitis Media.*

a. *Bureau of Drugs' Position.* The Bureau claimed that superior effectiveness of the estolate over the ethyl succinate cannot be seen from the available data. None of the studies compares erythromycin estolate with other erythromycin.

(1) The Bureau reviewed the results of two studies, which Lilly had in combining them, claimed showed that the estolate is more effective than the ethyl succinate in the treatment of *H. influenzae* otitis media (Ref. 72). In the first study, there was a cure rate of 77 percent with an ethyl succinate/sulfonamide combination, and a 50-percent cure rate with ethyl succinate alone. In the second study, there was a cure rate of 88 percent with an estolate/sulfonamide combination and an 81-percent cure rate with the estolate alone. The Bureau argued that the effectiveness of different drugs should be compared only when they are used in the same study.

(2) Contrasting results were obtained in another study comparing an estolate/sulfonamide combination and the estolate alone (Ref. 73). In this study, a 95-percent cure rate was obtained with the estolate/sulfonamide combination.

but only 63 percent of the patients treated with the estolate alone were cured.

(3) The investigators compared the effectiveness of an estolate/sulfonamide combination, and the estolate alone, among others (Ref. 74). They stated, "This study shows that the fixed combination of erythromycin estolate and triple sulfonamide suspenion is as effective in acute otitis media as the single drug ampicillin and more effective than the ingredients of the combination used separately."

(4) In another study, the effectiveness of erythromycin ethyl succinate/sulfonamide suspenion was compared with the effectiveness of the ethyl succinate alone, as well as with several other drugs (Ref. 75). The authors concluded that ampicillin, penicillin with sulfonamide, and erythromycin ethyl succinate/trisulfapyrimidine were the most bactericidal treatment.

(5) In still another study, the investigators compared the erythromycin concentration in middle ear exudate following estolate or ethyl succinate administration in eight patients with otitis media (Ref. 49). The concentration in the ethyl succinate group ranged from 0.24 to 1.02 mcg/mL with a mean of 0.84 mcg/mL. The concentration in the estolate group ranged from 1.68 to more than 8 mcg/mL, with a mean of 4.18 mcg/mL. The higher levels obtained with the estolate appear to be of little clinical significance as the patient with the highest serum and middle ear exudate levels of erythromycin had a moderate grouth of *H. influence* on the culture.

b. *Lilly's Position.* Lilly reviewed the results of the study comparing the ethyl succinate and an ethyl succinate/sulfonamide combination and its own study comparing the estolate and an estolate/sulfonamide combination (Ref. 72; described in the Bureau's paragraph (1) above). It was urged that, taken together, the studies indicate that the estolate is at least as effective in *H. influenzae* otitis media as a combination of the ethyl succinate and a sulfonamide.

4. *Diphtheria.*

a. *Bureau of Drug's Position.* The Bureau was aware of no data showing superior effectiveness of the estolate over other forms of erythromycin in the treatment of diphtheria.

(1) Many references to erythromycin therapy in diphtheria do not specify a particular form of the drug. The Report of the Committee on Infectious Diseases of the American Academy of Pediatrics (1977) states, under treatment of diphtheria, "Antimicrobial therapy is a valuable adjunct, but it is not a substitute for antitoxin. Penicillin and erythromycin are the drugs of choice." The Bureau cited nine other published articles generally recommending erythromycin in the treatment of diphtheria (Refs. 76 through 82, 115, and 119).

(2) Diphtheria carriers were treated with benzathine penicillin, erythromycin estolate, or clindamycin (Ref. 83). All treatments were successful; 92 percent of the patients in the estolate group had negative cultures at the end of treatment.

(3) Diphtheria carriers were treated with erythromycin estolate for 6 days (Ref. 84). All carriers with positive throat cultures before therapy developed negative cultures during therapy. Two weeks after the end of therapy, however, 21 percent of the patients had positive cultures again.

(4) This was a discussion of treatment in the 1970 diphtheria epidemic in San Antonio (Ref. 85). Children from 2 to 5 years old received erythromycin lactobionate intravenously or the ethyl succinate intramuscularly for 3 days, followed by the stearate for 4 days. Patients 6 years old and over received the lactobionate intravenously for 3 days and the stearate for the next 4 days. *C. diphtheriae* was eliminated from all patients.

Carriers were treated with estolate syrup for 7 days. There was a success rate of 89 percent.

(5) Of 142 carriers treated with procaine penicillin, 14 did not have the organism eliminated from the nasopharynx (Ref. 86). The patients who did not respond to penicillin were then given erythromycin ethyl succinate, which eliminated the organism in every patient.

(6) The Bureau reported on five published articles reporting on the successful use of erythromycin other than the estolate ethyl carbonate in the treatment of diphtheria (Refs. 87 through 91).

b. *Lilly's Position.* Lilly reviewed two literature excerpts (Refs. 83 and 84; reviewed by the Bureau in paragraphs (2) and (3) above) reporting on the estolate's effectiveness in eradicting diphtheria bacilli. The firm noted that other erythromycins have not been studied in the treatment of diphtheria.

5. *Pertussis.*

a. *Bureau of Drugs' Position.* The Bureau stated that there is no published evidence that one form of erythromycin is more effective than another in the treatment of pertussis (whooping cough).

(1) The Bureau reviewed nine excerpts from the medical literature which recommend erythromycin for the treatment of patients with pertussis or exposed to pertussis (Refs. 76, 78, 80, 92 through 96, and 115). No specific form of erythromycin is recommended.

(2) Erythromycin estolate eradicated *B. pertussis* from the nasopharynx in 2 to 7 days (Ref. 97). In the no antibiotic group, the organism was eliminated in 7 to 14 days. The estolate had no effect on the duration or severity of the disease, as judged by the length of hospitalization.

(3) All 131 patients treated with the estolate had negative nasopharyngeal cultures on the sixth day of treatment (Ref. 98). On the same day, 11 to 36 patients treated with ampicillin still had positive cultures.

(4) In an outbreak of pertussis, 200 patients (including 17 carriers) were treated with the ethyl succinate (Ref. 99). At the end of treatment, 118 patients (59 percent) were cured, and 62 (31 percent) were greatly improved. After 1 week of treatment, all 17 carriers had negative cultures.

(5) In this study patients received erythromycin as the ethylcarbonate or the stearate for 4 to 21 days (Ref. 100). The author simply noted that erythromycin seems to have prophylactic value in preventing or aborting whooping cough.

b. *Lilly's Position.* Lilly stated that eradication of *Bordetella pertussis* from the nasopharyngeal secretions of patients is important in reducing the occurrence of secondary cases and bacterial complications. In one study (Ref. 97; reviewed by the Bureau in paragraph (2) above) estolate treatment was superior to no treatment in reducing the length of time that nasopharyngeal cultures remain positive for *B. pertussis.*

Lilly asserted that the recent addition of the *B. pertussis* indication in the labeling of all erythromycin products was based on studies conducted only with the estolate. Through a freedom of information request, Lilly learned that the recommendation that the indication be approved was based on a review of published reports. Lilly asserts that only three of the published reports provided dosage information and identified the specific erythromycin product (Refs. 97, 98 and 99; reviewed by the Bureau in paragraphs (2), (3), and (4) above). Two of those three publications reported that the estolate was effective at a dosage of 40 to 50 mg/kg/day.

The third excerpt was a report of clinical experience with the ethyl succinate at a dose of 30 mg/kg/day. Lilly asserts that approval of the pertussis indication could not have been based on this study because, as stated by the reviewing medical officer, "It is not written in this paper how

evaluations of 'cured,' 'greatly improved' etc. were made . . . by the evaluation of clinical signs, duration of the disease or bacteriological results."

Lilly reported on a more recent excerpt stating that 7 days of ethyl succinate therapy at a dosage at 55 mg/kg/day failed to eradicate *B. pertussis* from an infant (Ref. 125; not reviewed by Bureau). A second infant who was exposed to the first patient contracted pertussis in spite of prophylactic use of ethyl succinate suspension at the same daily dose. The authors emphasized the need for further study.

6. *Legionnaire's Disease.*

a. *Bureau of Drug's Position.* The Bureau stated that different erythromycin preparations have been used in the treatment of Legionnaire's disease, but that data showing one erythromycin to be more effective than another were not available.

(1) The Bureau reviewed three literature excerpts recommending erythromycin for the treatment of Legionnaire's disease (Refs. 101, 102, and 115). Two of the articles recommend no specific type of erythromycin. One article states that the estolate should not be used because of the risk of hepatotoxicity.

(2) In this study, 15 of 16 patients treated with the lactobionate (intravenous) or stearate had a satisfactory response to therapy including seven who were administered immunosuppresive therapy concurrently (Ref. 99). One patient was not initially diagnosed as having Legionnaire's disease and was treated with penicillin, ampicillin, gentamycin, and oxacillin. He died on the tenth day of illness after receiving only two doses of erythromycin.

b. *Lilly's Position.* In severe infections or in patients with compromised host defenses, parenteral erythromycin therapy is often used in hospitalized patients. However, Lilly stated that in the management of outpatients with pneumonia that may be Legionnaire's disease, the use of an oral erythramycin product is recommended.

Studies in Detroit have demonstrated a lack of response to the stearate in spite of oral doses of 4 g or more daily (Refs. 121 and 122 not reviewed by the Bureau). One patient developed the disease while receiving the drug. Intravenous erythromycin at similar does resulted in therapeutic response.

Investigators at the University of Vermont also have emphasized the unpredictability of the stearate form in the initial treatment of Legionnaire's disease (Ref. 123; not reviewed by the Bureau).

Dr. Dolin, Professor of medicine at the University of Vermont, an individual who appeared at the hearing, noted that Legionnaire's disease is one of the few clinical situations in which erythromycin is the initial treatment of choice for a life-threatening infection.

Dr. Dolin stated that reliable absorption is a paramount consideration in selection of any oral therapy for a life-threatening disease. He reiterated the concern that absorption of oral erythromycin preparations other than the estolate is highly erratic and unreliable, particularly when taken without regard to meals, as is usually the case. He stated that he had observed several cases of Legionnaire's disease that progressed on oral base therapy, which eventually reponded to intravenous erythromycin therapy in the hospital.

Dr. Dolin stated that there are other properties of the estolate which suggest that it may have potential advantages in the treatment of Legionnaire's disease. Although it is argued that the propionyl ester is inactive, it is clear that significant antibacterial activity is associated with the ester and that hydrolysis to free base occurs continuously. In addition, the ester appears to achieve preferential penetration and concentration in macrophages, which are an important site of replication for Legionella organisms.

7. *Chlamydial Infections.*

a. Bureau of Drugs' Position. The Bureau stated there are no data demonstrating that one erythromycin is more effective than another in the treatment of chlamydial urethritis. In addition, the Bureau stated that there are no data demonstrating that one erythromycin is more effective than another in the treatment of chlamydial conjunctivitis or chlamydial pneumonia in neonates.

(1) Two literature excerpts recommend erythromycin (without specifying a particular form), to treat chlamydial pneumonia and chlamydial conjunctivitis (Refs. 105, 106, and 115).

(2) For chlamydial pneumonia, the authors suggest the use of systemic erythromycin, without specifying a particular form (Ref. 105). They suggest the use of systemic erythromycin ethyl succinate to treat chlamydial neonatal conjunctivitis.

(3) The Bureau reviewed two excerpts describing the successful use of the ethyl succinate in chlamydial pneumonia in children. (Refs. 107 and 108).

(4) A patient with chlamydial pneumonia who was treated unsuccessfully with other antibiotics responded well when the lactobionate was administered for 3 days, followed by the ethyl succinate for another 10 days (Ref. 109).

(5) Oral erythromycin estolate or topical erythromycin ointment was given to 36 infants with chlamydial conjunctivitis (Ref. 110). Of those patients, 35 had negative cultures on the seventh day. The systemic erythromycin was effective in eradicating *C. trachomatis* from the nasopharynx of six patients.

(6) This study compared the incidence of chlamydial infections in infants born to mothers with treated and untreated *C. trachomatis* cervical infections (Ref. 111). There was no infection among the infants of the 10 treated mothers treated with the base. Of the 20 infants born to untreated mothers, however, 6 developed chlamydial conjunctivitis, 2 developed chlamydial pneumonia, and 1 developed an asymptomatic nasopharyngeal infection.

b. *Lilly's Position.* Lilly stated that comparative studies of the estolate, base, and tetracycline in the treatment of nongonococcal urethritis due to *Chlamydia trachomatis* and/or *Ureaplasma urealyticum* were in progress (Ref. 124; not reviewed by the Bureau). There is not evidence that tetracycline resistance has been developing in strains of *U. urealyticum.* Therefore, it is important to establish which form of erythromycin will provide statisfactory alternate therapy.

8. *Campylobacter Enteritis.*

a. *Bureau of Drugs' Position.* The Bureau stated that there are no data comparing the effectiveness of the erythromycins in the treatment of campylobacter enteritis.

(1) Five literature excerpts recommed erythromycin treatment, but no particular form of erythromycin is specified (Refs. 112 through 116).

(2) Most of 37 children with campylobacter enteritis recovered spontaneously on conservative therapy (Ref. 117). However, seven children were treated with the estolate for relapse or persistent signs and symptoms of disease. Stool cultures became negative within 48 hours. Symptoms disappeared in five of the seven patients within 24 hours.

b. *Lilly's Position.* Lilly submitted no other data on the effectiveness of the estolate in camphylobacter enteritis.

## IV. References

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## V. Committee's Conclusions and Recommendations

On July 28, 1981, the Ad Hoc Advisory Committee on Erythromycin Estolate submitted written responses to the ten issues included in the February 27, 1981 notice of hearing. Some of the issues were modified by the Committee. The Committee responses are summarized below.

Before reaching specific issues, the Committee passed two resolutions: (1) "On the basis of available data, it is the conclusion of this Committee that no convincing evidence has been brought forward to indicate that the use of erythromycin estolate in children is associated with a higher incidence of cholestasis than other erythromycin formulations. As far as efficacy is concerned, the evidence clearly indicates that erythromycin estolate is as effective as other erythromycin formulations." (2) "The Committee finds the data available on erythromycin estolate hepatotoxicity adequate to estimate a risk of approximately one case per thousand exposures, but totally inadequate to determine the risk of other forms of erythromycin in adults. Serum levels with the estolate, whether evaluated as total drug or erythromycin base, are at least as good as with other dosage forms. Theoretical advantages of the estolate, such as superior tissue levels, penetration into alveolar macrophages, and perhaps initially more reliable absorption and bioavailability when the drug is taken with food (as is most likely in clinical practice) have been raised. These considerations lead the Committee to the conclusion that there is indeed a reason for the continued availability of the erythromycin estolate and the exercise of clinical judgment in evaluating the risk/benefit ratio of the particular erythromycin formulation to be used in each individual patient."

### *A. Adverse Reactions*

The Committee concluded that the incidence of hepatotoxicity for adults was greater for erythromycin estolate than for other erythromycins. The Committee concluded that the difference in the incidence of hepatotoxicty is of clinical concern.

The Committee unanimously voted that the incidence of hepatotoxicity in children was not greater for the estolate than for other erythromycins. Accordingly, the Committee made no finding on the clinical significance of the difference.

The Committee also found that the Bureau's voluntary adverse reaction reports to date did not determine the relative incidence for erythromycin adverse liver effects.

The Committee unanimously found that the data presented from the K–P study to date cannot reliably be used to determine the incidence of adverse liver effects for erythromycins. The Committee made no finding on the clinical significance of differences shown. The Committee unanimously found that a useful historical cohort study could be devised.

The Committee answered the question "Did the data presented from prospective clinical studies provide a reliable determination of the incidence of adverse liver effects for erythromycins?" by a vote of one positive, five negative, and five abstentions. The discussion preceding the vote indicates a concern over the conflicting results of the prospective clinical studies.

The Committee unanimously concluded that there are no major differences between erythromycin estolate and other oral erythromycins in the incidence of adverse effects in adults or in children, other than those involving the liver. One committee member described "no major difference" as the situation where there was a difference in one study in one direction but there is a slight difference in another study in the opposite direction.

### *B. Bioavailability*

The Committee unanimously concluded that it could not determine whether tissue concentration studies of the estolate and the ethyl succinate provide any evidence of a clinically significant advantage for adults or children because there is no valid interpretation of the clinical significance of bioavailability of the propionyl ester in tissue.

The Committee concluded that studies showing observable higher blood levels of erythromycin as the estolate indicate that the estolate is more reliably absorbed than other erythromycins. The Committee unanimously found, however, that it did not know whether blood levels of the estolate are related to the therapeutic response. It considered the ability of a medication to be taken without regard to meals as a clinical advantage.

The Committee unanimously agreed that all except one of the bioavailability studies in adults reviewed by the Bureau of Drugs demonstrate that blood levels of the base obtained following administration of erythromycin estolate are at least equal to those obtained after administration of erythromycin base, stearate, and ethyl succinate. For children, the unanimous response was that the erythromycin estolate suspension provides consistently higher blood levels measured as the base than does ethyl succinate suspension.

The Committee unanimously concluded it could not determine whether the propionyl ester of erythromycin estolate, apart from its being hydrolyzed, contributes to the therapeutic effect of erythromycin estolate. Accordingly, the Committee did

not determine whether the contribution of the propionyl ester to the therapeutic effect was of clinical significance.

The Committee unanimously concluded that a prospective study to determine the therapeutic effect of the propionyl ester may be needed. However, because such a study is not technically feasible at the present time, the Committee did not determine what the design of the study should be.

*C. Clinical Effectiveness*

The Committee concluded that erythromycin estolate has not been shown by means of randomized clinical trials to offer greater therapeutic effectiveness in adults over other erythromycins. The Committee also concluded that there is suggestive evidence that in some clinical circumstances erythromycin estolate may show therapeutic advantage in children over other erythromycins.

The Committee unanimously concluded as follows, "In the treatment of streptococcal pharyngitis in children, erythromycin estolate has been shown to be effective at a lower dose than that recommended for all other erythromycins. An ongoing prospective randomized clinical study shows superiority of the estolate over the ethyl succinate at 30 mg/kg/day given only twice a day. The lower dose and the less frequent dosing constitute a clinical advantage." The Committee made no findings on the effectiveness of various erythromycins in the treatment of primary syphilis.

The Committee unanimously concluded that neither erythromycin estolate nor erythromycin ethyl succinate is recommended alone for the treatment of *H. influenza* otitis media and that there have been no randomized, controlled clinical trials to show whether erythromycin estolate has any advantage over other erythromycins in the treatment of diphtheria, pertussis, Legionnaires' disease, chlamydial infections, or *Campylobacter* enteritis.

*D. Risk/Benefit Determination*

The Committee determined that the risk/benefit ratio of the estolate in adults is favorable, referring to the previously accepted resolution pertaining to adults. The Committee determined that the estolate has a favorable risk/benefit in children and referred to the previously accepted resolution pertaining to children. The Committee unanimously recommended two possible changes in labeling for adult dosage forms: (1) The wording "further, the propionyl ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cellular level" should be deleted from the labeling, and (2) indications of other infections, such as *Chlamydia trachomatis* and *Campylobacter*, should be added if data were submitted to support the added indications. The Committee also discussed whether the indications for chronic use, such as prophylaxis of rheumatic fever, should be removed, but took no vote on this issue.

The Committee recommended that the boxed warning in pediatric dosage forms of the estolate should have "ADULTS" juxtaposed to "WARNING". This would indicate that the data at this time do not justify a boxed warning for pediatric uses. The Committee unanimously recommended that the labeling changes suggested for the adult dosage forms be included in the pediatric dosage forms as well: (1) That the sentence stating that the estolate is hydrolyzed at the bacterial cellular level be deleted from the labeling; and (2) that indications for *Chlamydia trachomatis* and *Campylobacter* infections be considered as the data are submitted.

**VI. Comments on the Committee's Report**

The agency received three comments on the Committee's report—one each from HRG, the American Medical Association and Lilly.

1. HRG stated that the evidentiary findings of the Committee support the Bureau's arguments that erythromycin estolate tablets and capsules are unsafe, and that this requires the revocation of provisions for certification. In particular, HRG cites the findings of the Committee that greater hepatotoxicity is associated with the estolate and that this is of clinical concern.

Next, HRG stated that under the act, evidence of effectiveness must consist of adequate and well-controlled clinical investigations, citing *Weinberger* v. *Hynson, Westcott, and Dunning*, 412, U.S. 609, 629–630 (1972). HRG then asserted that the only benefits of the estolate over other erythromycins identified by the Committee were "theoretical . . . such as superior tissue levels, penetration into alveolar macrophages and perhaps initially more reliable absorption and bioavailability when taken with food." Finally, HRG argued that unless there are adequate and well-controlled clinical investigations showing greater benefits from the estolate than from other erythromycins, the agency is required by law to revoke the provisions for certification of the estolate tablets and capsules.

HRG urged the Commissioner to disregard the Committee's recommendation that the estolate remain on the market, stating that this issue is outside the Committee's mandate (none of the ten questions posed asked whether the estolate should remain on the market) and expertise. HRG maintained that it is only the Committee's factual findings, which it contended support revocation of certification provisions, that should be given weight in the Commissioner's deliberations.

HRG is correct that the Committee was not directly asked whether erythromycin estolate tablets and capsules should remain on the market. It was believed that the Committee's judgment on that issue would be clear from the answers to the ten questions posed. However, as the Committee's recommendation that the estolate remain on the market summarizes its risk/benefit evaluation, the Commissioner believes it proper for him to consider that recommendation in making his decision.

The Commissioner disagrees that the data presented compel the conclusion that the estolate has an unfavorable risk/benefit ratio. The Commissioner concludes that it is likely that the estolate is associated with hepatotoxicity to a greater extent than are other erythromycins. However, as explained in the following section, the Commissioner also finds benefits to offset this risk.

Moreover, the Committee concluded that available data tend to suggest benefits of the estolate compared to other erythromycins. The Committee's statements about the relative risks must be considered in this context. From the Committee's recommendation that the estolate be allowed to remain on the market, it clearly recognized that the crucial issue here is a weighing of risks and benefits, not an evaluation of the risks taken in isolation.

HRG misapplies the legal requirement that effectiveness must be demonstrated by adequate and well-controlled clinical investigations. Substantial evidence of the estolate's effectiveness was established at the time of its approval, and was not questioned in this proceeding. While the act requires proof of effectiveness derived from adequate and well-controlled clinical trials for pre-market approval, it makes no such requirement for safety evaluations. This is significant because this action fundamentally has been an inquiry into whether the risks of the estolate outweigh the benefits to such an extent that the certification provisions should be revoked on grounds of lack of safety. The effectiveness of the estolate is

relevant only insofar as it demonstrates sufficiently superior benefits over other erythromycins to offset the postulated greater risks of the estolate. In this type of consideration, data that are not derived from adequate and well-controlled clinical trials are not precluded from consideration.

In addition, the Commissioner disagrees with HRG that the only benefits associated with the estolate are theoretical. The Commissioner agrees with the Committee's conclusion that "the ability of a medication to be taken without regard to meals [is] a clinical advantage." On the other side of the scale, the Commissioner concludes that under conditions of actual use, the estolate is not less bioavailable than the other erythromycins as stated in the proposal. Thus, the benefits of the estolate are at least equal to the benefits of the other erythromycins.

2. The American Medical Association expressed its concern over the agency's "increasing tendency to evaluate both approved and new drugs on the basis of 'relative' safety and efficacy." It also argued that the agency should take no action against a drug unless controlled studies and experience demonstrate that a drug is not safe or effective. On the basis of the data presented, the Association concluded that the hepatotoxicity associated with the estolate is not of sufficient clinical significance and incidence to warrant revocation of provisions for certification, regardless of the estolate's bioavailability.

The Commissioner agrees that revocation of provisions for certification of erythromycin estolate tablets and capsules is not justified at this time. It must be emphasized however, that the act places the burden of proving the safety and effectiveness of a drug on those persons wishing to market it. Thus, the act does not require the agency to wait until a marketed drug is proven unsafe or ineffective before taking regulatory action but, rather, requires it to withdraw approval when there is evidence to suggest that a drug may no longer be considered safe and effective.

Further, as explained above, this matter is fundamentally an inquiry into the safety of the estolate, and the safety of any drug must be considered in the context of other drugs indicated for the same conditions. In a safety determination, the "relative efficacy" of a drug is relevant only insofar as it offsets the drug's risks, which otherwise may be considered unacceptable.

3. Lilly contended that the Committee reconfirmed its prior position that the estolate has a favorable risk/benefit ratio and should remain available for use. The company believed that the estolate had not been shown to be associated with a higher incidence of adverse hepatic effects, and that, because of its more reliable absorption, superior bioavailability, and better penetration of tissues and infection sites, the estolate offered important therapeutic advantages over other erythromycins. The firm recommended the prompt rescission of the proposal to revoke provisions for certification.

The Commissioner has concluded that revocation of certification provisions is not warranted at this time. The basis for this conclusion is set forth below.

## VII. Commissioner's Conclusions, Labeling

The Commissioner has evaluated all the data presented, weighing the risks and benefits of the estolate against the risks and benefits of other erythromycins. He has considered the recommendations of the Committee. The Commissioner accepts the Committee's recommendations that the adult and pediatric dosage forms of erythromycin estolate are safe, and that revocation of the certification provisions would be unjustified. In addition, he will take no action regarding the pediatric dosage forms. Accordingly, the December 4, 1979 proposal is withdrawn and the request made in HRG's petition is denied. The basis for the Commissioner's conclusion follows.

1. *The Risks.* In 1973, the Commissioner concluded that hepatotoxicity is associated only with the estolate. The data presented in this review of the estolate's safety indicate that all forms of erythromycin, adult and pediatric dosage forms, are associated with hepatotoxicity to some extent. Thus, the hepatotoxicity associated with the estolate may be of less significance than was thought in 1973, as it is now known that all forms of erythromycin can cause hepatotoxicity.

The Commissioner further concludes that the risk of hepatic reactions from any form of erythromycin in adults and children is quite small. In the Kaiser-Permanente study, for example, after examining the results of 3,661 courses of erythromycin therapy, the investigators were able to identify only one "probable" case and four "possible" cases of erythromycin-related hepatotoxicity.

The Commisssioner is unable to determine from the data presented in this proceeding the precise relative incidence of hepatic reactions caused by the various erythromycins. Although data obtained from the Bureau's ADR reporting system may be a useful post-marketing tool to estimate the relative incidence of adverse reactions in some cases, such estimates are imprecise in the present case. Lilly has raised the possibility of bias in the reporting of reactions resulting from the warnings in the labeling, "Dear Doctor" letters, and FDA *Drug Bulletins*. The Bureau's analysis of cases of hepatotoxicity, while demonstrating an approximate 25-fold greater number of cases in adults associated with the estolate than with other forms of erythromycin, cannot exclude the possibility that some or much of this difference is due to a reporting bias rather than to a true difference in adverse reaction rates. Neither can this reported 25-fold difference be dismissed on the basis of evidence offered by Lilly; the criticism that the data are flawed by a reporting bias is potentially valid but nevertheless is itself speculative and unproven. Thus, while an accurate estimate of the relative incidence of hepatic reactions associated with the various erythromycins cannot be made from the ADR reports, the Commissioner agrees with the Advisory Committee that the incidence of hepatotoxicity in adults is greater for the estolate.

Similarly, the reports of unnecessary surgery to relieve hepatic distress not known to be caused by the estolate could be subject to the same type of bias. There is no way to estimate the frequency of surgery to relieve hepatic distress actually caused by, but never attributed to, other erythromycins.

The examination of Medicaid data is a promising tool for post-marketing surveillance, and the Commissioner encourages its use. However, further analysis into the recordkeeping differences among States and the recordkeeping practices within a State under consideration must be conducted before inferences drawn can be relied upon.

Other data presented support the conclusion that the incidence of hepatic reactions is greater for the estolate than for other erythromycins. While none of the prospective clinical trials of hepatic reactions presented studied nearly enough patients to determine the actual incidence of cholestatic hepatitis, in many of the studies abnormal liver function tests were obtained from significantly more estolate patients than from non-estolate patients.

In addition, the in vitro data presented by Dr. Zimmerman were supportive. The data indicate that the estolate, but not the base, causes injury to Chang liver cells in suspension or culture, to suspensions of rat hepatocytes, and to isolated, perfused rat liver. The

Commissioner recognizes the difficulties inherent in applying in vitro data to in vivo phenomena. However, as with the abnormal liver function tests, the Commissioner believes that use of such data as supporting evidence is appropriate.

2. *The Benefits.* In 1973, the Commissioner concluded that the estolate was more bioavailable than other erythromycins. The estolate's greater bioavailability in comparison to other erythromycins was thought to result in comparable clinical effectiveness at lower doses in the treatment of streptococcal pharyngitis and primary syphilis. In 1981, the advisory committee also concluded that the estolate's lower dose and less frequent dosing in the treatment of streptococcal pharyngitis in children constitute a clinical advantage of the estolate.

The Commissioner does not agree with either the 1973 conclusion or the current committee's conclusion that the estolate is more effective than other erythromycins in the treatment of streptococcal pharyngitis. When proper dosages are used the cure rates of all the erythromycins are similar. The fact that lower doses of the estolate can be used would be considered a benefit only if fewer adverse effects were associated with lower doses, but this has not been shown. The data on gastrointestinal side effects are contradictory and no conclusions can be drawn from them. As explained above, the incidence of hepatic reactions are greater for the estolate than for other erythromycins.

The Commissioner disagrees with the previous finding regarding primary syphilis. The studies on which the conclusion that the estolate is more effective was based examined 12-month re-treatment rates, rather than microbiological effectiveness at the end of treatment. It is obvious that a number of factors other than treatment effectiveness will affect the re-treatment rate. No other data on the effectiveness of the various erythromycins in treating syphilis were presented in this proceeding. Thus, the Commissioner concludes that no difference among erythromycins in the treatment of syphilis has been shown.

Data intended to demonstrate the greater effectiveness of the estolate in the treatment of Legionnaire's disease were also presented. However, these data were not comparative, and no conclusions can be drawn from them. The Commissioner is aware that a comparative study of Legionnaire's disease is ongoing, but whether a clinical advantage for the estolate will be shown cannot, of course, be determined at this time.

In addition, data on diphtheria, pertussis, chlamydial infections and campylobacter enteritis were presented. These data are inconclusive and inadequate to demonstrate an advantage of one erythromycin over another.

Further, the Commissioner disagrees with both the 1973 conclusion that the estolate is more bioavailable than other erythromycins as well as the Bureau's assertion in 1979 that in terms of free base, the estolate is less bioavailable than other erythromycins. Studies presented by the Bureau in this proceeding indicate that under fasting conditions the estolate achieves significantly lower blood levels than other erythromycins, particularly in the first doses. These studies also indicate, however, that under nonfasting conditions, in terms of free base, the solid dosage forms of the various erythromycins are essentially bioequivalent. The Commissioner acknowledges that in actual practice, drugs are often taken with meals. Thus, there is no evidence of any additional benefit, or any additional disadvantage, accruing to the estolate because of its bioavailability.

There has been no dispute that in terms of free base, the estolate suspension is significantly more bioavailable than the ethyl succinate suspension. No clinical benefit has been shown to result.

At this time, no conclusions can be drawn concerning the tissue levels of free base. It has not been demonstrated that the various erythromycins are hydrolyzed to free base in tissue to the same extent that they are in the blood. Thus, it is not clear that higher tissue levels of free base are in fact obtained with the estolate. Further, there has been no demonstrated clinical advantage to the presumed higher tissue levels.

In addition, the data presented are inadequate to determine the validity of the theory that the propionyl ester acts as a delivery system to the bacterial cell as well as functioning as a reservoir out of which free base is hydrolyzed. Similarly, at this time there are no data demonstrating that the propionyl ester is in fact hydrolyzed to free base within bacterial cells and alveolar macrophages.

The lack of greater clinical effectiveness or greater bioavailability does not lead to the conclusion that there are no greater benefits associated with the use of the estolate. The greater benefit is due to the estolate's reliability of absorption.

The Bureau and Lilly both stated that the estolate is more reliably absorbed initially than the base when taken with food. In addition, Lilly noted that the investigators in the University of Texas studies concluded that the absorption of the stearate is decreased when it is taken shortly after a meal. The Committee concluded, and the Commissioner agrees, that the estolate's reliable absorption when taken with food is a clinically significant advantage that cannot be overlooked, particularly in potentially fatal diseases, such as Legionnaire's disease. This characteristic of the estolate is quite striking when compared to the absorption of the base under non-fasting conditions—7 out of 24 patients failed to obtain any blood level whatsoever for 6 hours after drug administration. Free base from the estolate was present in all estolate patients three hours after drug administration. (It must also be noted that the ethyl succinate's absorption is unaffected by food.)

3. *Risk/Benefit Determination.* The Commissioner concludes, as in 1973, that the risk/benefit ratio of erythromycin estolate, in both adult and pediatric dosage forms, is favorable. Thus, the Commissioner disagrees with the Bureau's 1979 assertion that the estolate has an unfavorable risk/benefit ratio.

The risk of hepatotoxicity is greater from the estolate than from other erythromycins, but the actual risk of any one patient incurring an hepatic reaction is quite small. Further, the reaction, though unpleasant, has never resulted in a fatality.

The Bureau asserted that the estolate is less bioavailable than other erythromycins. The Bureau had tentatively concluded that this, taken with the greater hepatotoxicity associated with the estolate, was sufficient to unfavorably alter the risk/benefit ratio. The Commissioner now concludes that the erythromycins are essentially bioequivalent. Thus, while the bioavailability of the estolate compared to other erythromycins cannot be counted as a benefit as in 1973, neither can it be considered a detriment.

Similarly, the clinical effectiveness of the estolate compared to other erythromycins cannot be considered either a risk or a benefit. The data presented demonstrate no differences among the various erythromycins in clinical effectiveness.

The clearly demonstrated benefit of estolate administration is its reliable absorption when taken with food. This is of particular benefit in serious diseases. Thus, the Commissioner concludes that the estolate's relatively greater risk of hepatotoxicity is offset by its relatively greater reliability of absorption.

The data presented in this proceeding have been set forth in detail. They are voluminous and conflicting. The Commissioner believes, however, that the data support the continued marketing of the estolate, which will allow practitioners to select the most appropriate drug for each individual patient.

4. *Labeling.* Labeling changes are set forth in a related document published elsewhere in this issue of the **Federal Register**. The changes are explained in this notice for information purposes.

The Committee recommended that the pediatric dosage form (oral suspension, chewable tablets, and pediatric drops) of the estolate juxtapose the word "ADULTS" and "WARNING" above the black box warning. This would indicate that the warning box applies to adults only, not to children. The Commissioner disagrees with this recommendation because data were presented indicating that hepatic reactions do occur in children. The risk of hepatic reactions in children has been known for some time to be far smaller in children than in adults. The data presented at this hearing do not justify any change in the boxed warning. Thus, no change in the current boxed warning is required.

The Committee also recommended deletion from the labeling of all dosage forms the wording "(f)urther, the propionyl ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cellular level." The Commissioner agrees. No data demonstrating that the propionyl ester is hydrolyzed at the bacterial cell level were presented.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502, 507, 52 stat. 1041, 1050–1051 as amended, 59 stat. 463 as amended, (21 U.S.C. 321(n), 352, 357)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10 (formerly 5.1: see 46 FR 26052; May 11, 1981)).

Dated: May 18, 1982.

**Arthur Hull Hayes, Jr.,**

*Commissioner of Food and Drugs.*

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## DEPARTMENT OF HOUSING AND URBAN DEVELOPMENT

### Office of Assistant Secretary for Housing—Federal Housing Commissioner

### 24 CFR Part 203

[Docket No. R-82-979]

### Mutual Mortgage Insurance and Rehabilitation Loans

*Corrections*

In FR Doc. 82-12792 appearing on page 20149 in the issue of Tuesday, May 11, 1982; on page 20151, make the following changes:

(1) In column one, § 203.264(b), fifth line, "after" should read "before".

(2) In column three, the third bold face heading now reading "§§ 203.275 through 203.309 [Removed]". should read "§§ 203.305 through 203.309 [Removed]".

BILLING CODE 1505-01-M

## DEPARTMENT OF THE INTERIOR

### Office of Surface Mining Reclamation and Enforcement

### 30 CFR Part 906

### Abandoned Mine Land Reclamation Program

**AGENCY:** Office of Surface Mining Reclamation and Enforcement (OSM), Interior.

**ACTION:** Receipt of the Abandoned Mine Land Reclamation (AML) Grant Application from the State of Colorado.

**SUMMARY:** On April 29, 1982, the State of Colorado submitted to OSM its proposed abandoned mine land reclamation grant application under the Surface Mining Control and Reclamation Act of 1977 (SMCRA). OSM is seeking public comment on the adequacy of the State grant application. The grant will not be approved until the Secretary has approved the Title IV Reclamation Program.

**DATES:** Written comments on the application must be received on or before 5:00 p.m. June 24, 1982.

**ADDRESSES:** Copies of the full text of the proposed Colorado grant application are available for review during regular business hours at the following location: Office of Surface Mining Reclamation and Enforcement, New Mexico State Office, 219 Central Avenue, NW., Suite 216, Albuquerque, New Mexico 87102.

Written comments shoud be sent to: Robert H. Hagen, State Director, New Mexico State Office, 219 Central Avenue, NW., Suite 216, Albuquerque, New Mexico 87102.

**FOR FURTHER INFORMATION CONTACT:** Robert H. Hagan, State Director, New Mexico State Office, 505/766-1486, Same address as above.

**SUPPLEMENTARY INFORMATION:** On February 16, 1982, a State reclamation plan was submitted to the Secretary. The Colorado Plan is presently being reviewed by the Secretary. Under section 405(f) of the SMCRA, the Secretary cannot approve a State AMLR program grant unless that State has an approved State AMLR program pursuant to section 405(d) of the SMCRA.

On April 29, 1982, OSM received an AMLR grant application from the State of Colorado.

Title IV of the Surface Mining Control and Reclamation Act of 1977 (SMCRA), Public Law 95-87, 30 U.S.C. 1201 *et seq.*, establishes an AMLR Program for the purposes of reclaiming and restoring land and water resources adversely affected by past mining. This program is funded by a reclamation fee imposed upon the production of coal. Lands and water eligible for reclamation under the program are those that were mined or affected by mining and abandoned or left in an inadequate reclamation status prior to August 3, 1977, and for which there is no continuing reclamation responsibility under State and Federal law.

Each State having within its borders coal mined lands eligible for reclamation under Title IV of SMCRA may submit to the Secretary a State reclamation grant application to implement the provisions of the approved State Reclamation Plan. However, grants for reclamation may be issued only to States with an approved Title V Regulatory Program for active mine reclamation and an approved Title IV Reclamation Program. The grant application received from the State of Colorado will be reviewed and held pending a final approval by the Secretary on the State's Title IV program in accordance with SMCRA.

This notice describes the nature of the proposed projects and sets forth information concerning public participation in the development of the projects. This publication does not represent any decision by the Secretary on the Title IV Reclamation Program, but is published solely for the purpose of expediting the review process and the implementation of the reclamation program if the Title IV program of the State of Colorado is approved.