DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[21 CFR Part 342]

[Docket No. 76N-0482]

OVER-THE-COUNTER DRUGS

Establishment of a Monograph for OTC Topical Antibiotic Products

AGENCY: Food and Drug Administration (FDA).

ACTION: Proposed Rulemaking.

SUMMARY: FDA proposes to establish conditions under which over-the-counter (OTC) topical antibiotic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the FDA's Advisory Review Panel on OTC Antimicrobial (II) Drug Products.

DATES: Comments by June 30, 1977.

FOR FURTHER INFORMATION CONTACT:

William D. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: Pursuant to Part 330 (21 CFR Part 330), the Commissioner of Food and Drugs received on October 29, 1976, a report of the Antimicrobial Panel on topical antibiotic drugs. In accordance with § 330.10 (a) (6) (21 CFR 330.10(a) (6)), the Comcissioner is issuing (1) a proposed regulation containing the monograph recommended by the Panel establishing conditions under which OTC topical antibiotic drugs are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph on the basis of a determination by the Panel that the available data are insufficient to classify such conditions under either (1) or (2) above; and (4) the conclusions of the Panel and recommendations to the Commissioner. The summary minutes of the Panel meetings are on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857.

The purpose of issuing the unaltered conclusions and recommendations of the Panel is to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The Commissioner has not yet fully evaluated the Panel's report, but has concluded that it should first be issued as a formal proposal to obtain full public comment before any decision is made on the Panel's recommendations. The report represents the best scientific judgment of the members of the Panel. The report has been prepared independently of FDA and does not necessarily reflect the agency position on any particular matter addressed therein. After careful review of all comments submitted in response to this proposal, the Commissioner will issue a tentative final regulation in the FEDERAL REGISTER to establish a monograph for OTC topical antibiotic drug products.

In accordance with § 330.10(a) (2) (21 CFR 330.10(a) (2)), all data and information concerning OTC topical antibiotic drug products submitted for consideration by the Panel have been handled as confidential by the Panel and FDA. All such data and information shall be put on public display at the office of the Hearing Clerk, Food and Drug Administration, on or before May 2, 1977, except to the extent that the person submitting specific data demonstrates that they still fall within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality shall be submitted to FDA, Bureau of Drugs, Division of OTC Drug Products Evaluation (HFD-510), 5600 Fishers Lane, Rockville, MD 20857.

Based upon the conclusions and recommendations of the Panel, the Commissioner proposes, upon publication of the final regulation:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify such conditions either as Category I—generally recognized as safe and effective and not misbranded, or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for not longer than 2 years (for the specific conditions discussed in this document) after the date of publication of the final monograph in the FEDERAL REGISTER, provided studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel are conducted. The period of time within which studies must be completed will be carefuly reviewed by the Commissioner after receipt of comments on this document and will probably be shortened.

The Commissioner has reviewed the conclusions and recommendations of the Panel regarding skin wound protectants. He notes that the Panel's definition and criteria are not identical to those previously proposed by the Antimicrobial I Panel as published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33140). The Commissioner advises that he will respond, in a tentative final monograph (21 CFR Part 333) to be published in a later issue of the FEDERAL REGISTER, to the comments regarding the previous proposal made by the Antimcriobial I Panel, and clarify the definition, criteria, and testing procedures pertaining to skin wound protectants. He invites full public comment on this proposal, and on the tentative final monograph after it is published in the FEDERAL REGISTER.

The Commissioner has also reviewed the conclusions and recommendations of the Panel pertaining to finished dosage forms and the Panel's proposal in the monograph to limit dosage forms to the use of ointment preparations only. At this time, the Commissioner seeks comment on this proposal and on the agency's current limitation of cream preparations to prescription use only.

The Commissioner has reviewed the potential environmental impact of the recommendations and proposed monograph for OTC topical antibiotic products of the Panel on Review of Antimicrobial Agents and has concluded that the Panel's recommendations and proposed monograph will not significantly affect the quality of the human environment and that an environmental impact statement is not required.

The conclusions and recommendations in the report of the Antimicrobial Panel for topical antibiotic drugs follow:

In the FEDERAL REGISTER of January 5, 1972 (37 FR 85), the Commissioner announced a proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels. On May 8, 1972, the Commissioner signed the final regulations providing for the OTC drug review under § 330.10, published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464), which were made effective immediately. Pursuant to these regulations, the Commissioner issued a request for data and information on antimicrobial active ingredients for the treatment or prophylaxis of specific disorders such as seborrhea, dandruff, acne, athletes foot, vaginitis, and otitis externa (swimmers ear), in the FEDERAL REGISTER of December 16, 1972 (37 FR 26842). A subsequent request for data and information was published in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391) for topical antibiotic drugs used in OTC products for treatment and prevention of infections in minor skin wounds.

The Commissioner appointed the following panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of the antimicrobial agents, including antibiotic ingredients, pursuant to § 330.10(a) (1):

Wallace Guess, Ph.D., Chairman
Frank B. Engley, Jr., Ph.D.
Paul D. Stolley, M.D., M.P.H.
William F. Schorr, M.D.
W. Kenneth Blaylock, M.D.
E. Dorinda Loeffel, M.D.
Margaret Hitchcock, Ph.D., who resigned from the Panel in September 1974 and was replaced by David R. Brown, Sc.D.; Dr. Brown resigned in March 1976 and was replaced by Eula Bingham, Ph.D.

The Panel was first convened on July 26 and 27, 1974, in an organizational meeting. Working meetings have been held :(1) In 1974 on September 13, 14, and 15; October 18, 19, 20; (2) in 1975 on January 10, 11, and 12; February 21, 22, and 23; March 21, 22, and 23; April 18, 19, and 20; May 16, 17, and 18; June 27, 28, and 29; July 24, 25, and 26; September 5, 6, and 7; October 3, 4, 5, and 31; November 1 and 2; (3) in 1976 on January 9, 10, and 11; February 13, 14, and 15; March 12, 13, and 14; May 14, 15, and 16; June 25, 26, and 27; July 23, 24, and 25; August 20, 21, and 22; October 29. Portions of the meetings from October 1975 were devoted to the review of ingredients for treating athletes foot.

Three nonvoting liaison representatives served on the Panel. Ms. Sarah Newman, nominated by an ad hoc group of consumer organizations, served as the consumer liaison. James Lawrence, M.D., Ph.D., nominated by the Proprietary Association, and Gavin Hildick-Smith, M.D., nominated by the Cosmetic, Toiletry and Fragrance Association, served as the industry liaisons .

The following employees of the Food and Drug Administration served: Mary K. Bruch, Executive Secretary; Michael Kennedy, Panel Administrator until July, 1974, followed by Armond Welch, R.Ph.; Melvin Lessing, R.Ph., M.S., Drug Information Analyst until October, 1974, followed by Joseph Hussion, R.Ph., until July, 1976, and Mary Ann Bukovinsky until August, 1976.

The following individuals were given an opportunity to appear before the Panel to express their views either at their own or at the Panel's request:

Violet Anderson, Ph.D.
Clealand F. Baker
Stanley Bushby, Ph.D.
Hugh Dillon, M.D.
Maxwell Findland, M.D.
James Leyden, M.D.
David Rovee, Ph.D.
Robert Scheuplein, Ph.D.
Alex Steigman, M.D.
Frances Storrs, M.D.
Marion Sulzberger, M.D.
David Taplin

No person was denied an opportunity to appear before the Panel.

The Panel thoroughly reviewed the various data submissions and available literature; listened to additional testimony from interested parties, including invited consultants; and considered all pertinent data and information submitted in arriving at its conclusions and recommendations

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to these classes of drugs are set out in three categories:

Category I. Conditions under which topical antibiotic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which topical antibiotic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends the following for each category of drugs:

1. That the conditions included in the monograph on the basis of the Panel's determination that they are generally recognized as safe and effective and are not misbranded (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER, regardless of whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient (Category III) to classify them either as Category I—generally recognized as safe and effective and not misbranded; or as Category II—not being generally recognized as safe and effective or would result in misbranding, be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised by the Panel.

I. SUBMISSION OF DATA AND INFORMATION

Pursuant to the notice published in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391) requesting the submission of data and information on OTC topical antibiotic drugs, the following firms made submissions relating to marketed products:

A. SUBMISSION BY FIRMS

Firm:	*Marketed products*
Burroughs-Wellcome Co., Research Triangle Pk., NC 27709.	Neosporin Ointment.
Day-Baldwin, Inc., Hillside, NJ 07256.	Bacitracin Ointment, Bacitracin-Neomycin Ointment, "3" Antibiotic Ointment, Neomycin Ointment.
The Dow Chemical Co., Zionsville, IN 46077.	Neo-Polycin.
Lederle Laboratories, Pear River, NY 10965.	Achromycin Ointment, Aureomycin Ointment.
Merrell-National Laboratories, Cincinnati, OH 45215.	Bacimycin Ointment.
Pfizer Pharmaceuticals, New York, NY 10017.	Bacitracin Antibiotic Ointment, Terramycin Ointment with Polymyxin B Sulfate, Terramycin with Polymyxin B Sulfate Topical Powder.
E. R. Squibb & Sonth, Inc., New Brunswick, NJ 08903.	Spectrocin Ointment.
The Upjohn Co., Kalamazoo, MI 49001.	Baciguent Ointment, Myciguent Cream, Myciguent Ointment, Mycitracin Ointment.

B. LABELED INGREDIENTS CONTAINED IN MARKETED PRODUCTS SUBMITTED TO THE PANEL

Bacitracin
Chlortetracycline hydrochloride
Fuzene base
Glyceride wax
Gramicidin
Lactose
Lanolin
Mineral oil
Neomycin sulfate
Oxtetracycline hydrochloride
Petrolatum
Polyethylene glycol
Polymyxin B sulfate
Tetracycline hydrochloride
Zinc bacitracin

C. CLASSIFICATION OF INGREDIENTS.

The Panel has classified the following ingredients submitted to the Panel into groups identified below:

1. *Ingredients identified as active antibiotic ingredients.*

Bacitracin
Chlortetracycline hydrochloride
Gramicidin
Neomycin sulfate
Oxytetracycline hydrochloride
Polymyxin B sulfate
Tetracyline hydrochloride
Zinc bacitracin

2. *Ingredients submitted to the Panel and identified as inactive and/or pharmaceutically necessary ingredients.* Inactive ingredients are useful in the manufacturing of pharmaceutical preparations or in enhancing the quality and/or appearance of the product. The Panel advocates the listing of all inactive ingredients on the product label. In topical medications, many of the labeled inactive ingredients are vehicles into which the active ingredients are incorporated. These vehicles, including ointment and cream bases, play a vital role in release and delivery of active ingredients into the skin. The other inactive substances are added to enhance product appearance and/or quality.

The list below reflects only those inactive ingredients contained in the labeled ingredients submitted to the Panel and is not intended to be an exhaustive list.

Fuzene base
Lactose
Lanolin
Mineral oil
Petrolatum
Polyethylene glycol

3. Antibiotic ingredients combined with nonantibiotic active ingredients. The Panel has neither received nor reviewed any data concerning combinations of antibiotic ingredients with active nonantibiotic ingredients.

The Panel is aware that future topical products may be developed combining the above antibiotics with active ingredients such as corticosteroids, antihistamines, anesthetics, antifungal agents, and other antibiotics not reviewed by the Panel. The Panel concludes that such combinations should be subject to appropriate FDA review procedures prior to OTC marketing.

II. General Statements and Recommendations

A. General Comment

The Panel was charged with the review and evaluation of safety and effectiveness data on antimicrobil and antibiotic agents and combinations in topically applied OTC drug products. This charge included recommendations about appropriate permitted labeling, with guidelines for warnings, precautions, contraindications, and directions for use.

The Panel has defined an "antimicrobial ingredient" as an agent that kills or inhibits the growth and reproduction of microorganisms. A chemical substance produced by a microorganism and having the capacity, in dilute solutions, to kill or inhibit the growth of other microorganisms is called an "antibiotic." Antibiotics kill at different rates. Whether one considers it bacteriostatic (to inhibit the growth or reproduction of bacteria) or bactericidal (to kill bacteria) may depend entirely on the rate of kill because the definition is based on different rates of kill. As with most biological/chemical phenomena, there is a gradation between physical or chemical factors that kill organisms rapidly and those that prevent organisms from growing or multiplying without their rapid destruction. Factors such as concentration of chemical, temperature, presence of organic matter, and the inherent susceptibility of the type of organism or strain of organism can affect the rate of kill. Thus, chemicals that kill organisms rapidly under the conditions of test or study are called "cidal," and those that kill the organisms very slowly or suppress reproduction are referred to as "static". The final descriptive term used may reflect the actual rate of kill or the adequacy of the procedure used to test for killing ability. In the in vivo or clinical situation, static antibiotics may prevent organisms from growing or reproducing so that the body defense mechanism are able to destroy the organisms. Under such conditions, clinical effectiveness may be found with static types of drugs.

The definition of an antibiotic drug stated in section 507 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 357) is as follows:

> * * * the term "antibiotic drug" means any drug intended for use by man containing any quantity of any chemical substance which is produced by a microorganism and which has the capacity to inhibit or destroy micro-organisms in dilute solution (including the chemically synthesized equivalent of any such substance).

"Pathogenic" bacteria are microorganisms capable of causing infection, particularly when introduced into an area of injured or abnormal skin. There are microorganisms in, on, and all around the human body. Most of these organisms are nonpathogenic residents on the skin and are referred to as "normal flora."

Of interest to the Panel are skin infections that are frequently grouped together under the term "pyoderma," which indicates the presence of pus in the skin. In addition to containing pus, infected skin is usually red, warm, and sore (painful or tender). Pyoderma includes both "primary infections" which develop on previously normal or uninjured skin, and "secondary infections" which develop in preexisting skin lesions such as poison ivy dermatitis, chronic leg ulcers, or burns.

Primary skin infections include such common conditions as impetigo and boils, caused predominantly by the gram-positive bacteria, Staphylococcus aureus and/or Streptococcus pyogenes (Group A beta-hemolytic streptococcus). "Impetigo" is a contagious, superficial pyoderma, common in children, which is caused by either staphylococci and/or streptococci and begins with blisters, which rupture to form thick, yellowish-red scabs (crusts). "Ecthymas", usually caused by streptococci, are another type of superficial pyoderma, with scabs overlying shallow, purulent ulcers that develop most commonly on the legs following insect bites. Primary infections, which develop around hair follicles, are caused by staphylococci. This type of skin lesion is called "folliculitis" when only small superficial pustules are present, but is called a "boil" or "furuncle" if a deep, red, tender swelling with a core of pus develops. A furuncle is a specialized type of skin abscess or a well-circumscribed collection of pus. Another type of staphylococcal abscess, known as acute paronychia, develops around a fingernail or toenail and consists of a red, tender swelling containing pus.

Secondary infections develop in skin that is damaged by factors such as vigorous scratching, excessive moisture, or poor circulation. Pathogenic staphylococci and streptococci presumably penetrate the skin through the scratching of insect bites, poison ivy dermatitis, or other itchy eruptions. People with "atopic eczema," an inherited itchy dermatitis that usually begins in infancy, frequently develop secondary infections similar to impetigo. Older patients with atopic eczema confined to the hands also develop recurrent secondary infections on the hands, known as infected "hand eczema." Ear piercing also predisposes to secondary infection, particularly if complicated by simultaneous allergy to the nickel component of metal earrings touching the ear lobes.

Secondary infections involving microorganisms other than staphylococci or streptococci develop in certain predisposed skin areas. Pseudomonas aeruginosa, a type of gram-negative bacteria, thrives on warm, moist skin surfaces such as the groin, ear canal, underarm areas and toewebs. Although its role in causing secondary infection in these areas is controversial, Pseudomonas is a pathogen capable of causing death in patients with extensive and deep burns. Pseudomonas species as well as other microorganims may be found in chronic leg ulcers due to varicose veins or poor arterial circulation. The role of microorganisms in delay of healing of these deep, rounded ulcerations above the ankle, remains uncertain. The role of microorganisms is also unclear in "bed sores" or "decubitus ulcers" in bedridden patients.

Organisms, other than those discussed above, may also be invovlved in wound infection but are not common in minor wounds.

While some the aforementioned antibiotics are used extensively for serious injuries and burns on the advice of physicians, the Panel will deal only with the limited OTC uses of these ingredients. The Panel will, therefore, limit its review in this document to those topical antibiotic ingredients that are generally promoted to help prevent infection and aid healing when applied to minor skin cuts, abrasions, and burns.

B. Introduction, History and Development of Regulation of Antibiotics by FDA

The antibiotic era of chemotherapy was launched in the 1930's with the work of Dubos on tyrothricin; Waksman on streptomycin; and Fleming, Chain, and Florey on penicillin. Historically, the regulation of antibiotic drugs began when the Federal Food, Drug, and Cosmetic Act was passed in 1938, requiring that drugs be precleared by FDA and that proof of safety be shown prior to marketing. Between 1938 and 1962, approximately 10,000 new drug applications (NDA's) were approved for drug formulations. Among this total were several NDA's for antibiotics.

The therapeutic application of antibiotic substances developed during the World War II era. When these new antibiotic drugs suddenly became generally available for use against both bacterial and fungal infections, physicians focused new attention on specific etiologic agents of infectious diseases and their relative susceptibilities to new antimicrobial agents. The search for antibiotic drugs with broad antimicrobial spectra and minimal toxicity to the patient continued. Instead of abandoning use of a drug when toxicity became

apparent, efforts were made to alter drug toxicity while preserving antimicrobial activity.

Some antibiotics that were found to be too toxic in systemic use were tested, studied, and approved for topical therapy. Because of the limited antimicrobial spectrum of each antibiotic, several were often combined in commercial preparations to cover the spectrum of organisms usually found in infections of the skin.

As antibiotics came into use, it was realized that their potency and purity were quite variable because they were manufactured through a biological fermentation process. Pharmaceutical control of potency and purity of fermentation products developed slowly and was not as exact as that of chemically synthesized drugs. Consequently, beginning in 1945 with penicillin, and later extending to four other antibiotics, section 507 of the act (21 U.S.C. 357) was modified to require certification of each production batch of these antibiotics under a specific monograph published in the Code of Federal Regulations. Included among the four antibiotics were bacitracin, which was certified for topical OTC use in 1948, and chlortetracycline, which was certified for prescription use, also in 1948. Thus, in addition to submitting a new drug application, the manufacturer was required to supply FDA with batches of the antibiotic for certification prior to marketing. The specific monograph for each antibiotic delineated the tests required and limits to be met prior to marketing (21 CFR Part 436).

By 1953, several NDA's were approved for topical antibiotics. After a few years, firms proposing to market these antibiotics were informed by FDA that these drugs were no longer considered "new" drugs and therefore did not require the submission of a new drug application prior to marketing. However, the removal of the NDA requirement did not change the firms' need to obtain certification of each antibiotic batch. Numerous products containing antibiotics then appeared on the market without NDA's.

In 1962, Congress passed the Kefauver-Harris Amendments to the act. In general, these amendments required that substantial evidence of effectiveness as well as safety be submitted to FDA for any drug, and they also expanded the requirement of certification to all antibiotics intended for human use.

A notice of proposed rule making for certification procedures of specific antibiotics was adopted (21 CFR Part 431). To implement this procedure, an Antibiotic Task Force was formed within FDA. Over a period of approximately 6 months, this group reviewed specific drug products and made recommendations as to their safety and effectiveness. In this review, some antibiotics were not recognized as safe or effective and letters were sent to the manufacturers informing them to the task force's stand. A final order stating definitions and certification procedures for these antibiotics not recognized as safe and effective was published in the FEDERAL REGISTER of March 9, 1966 (31 FR 4129). Only after implementation of the recommendations of the task force were the affected antibiotics again certified.

Also as a consequence of the mandate of the 1962 amendments to the act, the Commissioner requested assistance from The National Academy of Sciences and The National Research Council (NAS/NRC) in evaluating the effectiveness of all drug products approved for safety between 1938 and 1962. This review included topical antibiotic products. The resulting Drug Efficacy Study Implementation (DESI) reports of the NAS/NRC provided recommendations to help the Commissioner in making a decision about the effectiveness of individual drug products.

Both OTC and prescription antibiotics and antibiotic combinations were evaluated in the DESI review. The overall conclusions were made for each product rather than for the class or the ingredients. Many topical antibiotic formulations were declared less than effective on the basis of lack of controlled clinical studies to show effectiveness. However, certain combinations of prescription antibiotics were declared effective. Studies to demonstrate the effectiveness of some other combinations are currently being designed and executed to satisfy DESI requirements (particularly the anti-infective/steroid combinations as published in the FEDERAL REGISTER of October 9, 1974 (39 FR 36365)). Time has elapsed since the NAS/NRC review and additional data have become available for topical antibiotics. In order to have a comprehensive OTC review, the Commissioner requested that the Panel review all topical antibiotic ingredients marketed as OTC for both safety and effectiveness.

C. DEFINITIONS OF PRODUCT CATEGORIES

The panel concludes that OTC topical antibiotic products should be used only as part of the first-aid treatment of small superficial wounds such as cuts, abrasions, and burns. The Panel considered the first-aid treatment of small superficial wounds as a process that includes initial adequate cleansing that may or may not be followed by application, of a safe, nonirritating product that does not interfere with normal wound healing and may reduce bacterial numbers and help prevent infections.

The following definitions of topical antibotic categories have been developed by the Panel in an attempt to simplify categorization of ingredients and eliminate labeling confusion.

1. Skin wound protectant. A safe, nonirritating preparation applied to small cleansed wounds that provides a protective physical barrier, conforming to the barrier testing for skin wound protectants as published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33140), and may also include a chemical (antibiotic), which neither delays healing nor favors the growth of microorganisms.

2. Skin wound antibiotic. A safe, nonirritating antibiotic-containing preparation that prevents or treats overt skin infection. Claims stating or implying an effect against microorganisms must be supported by controlled human studies that demonstrate prevention or effectiveness in the treatment of infection.

D. ADVERTISING AND CONSUMER USE OF TOPICAL ANTIBIOTICS

The Panel recognizes that topical medications for treatment of minor cuts, burns, and abrasions are useful to the general public. It believes that such medications should be available "over-the-counter," provided they are safe and effective. The Panel is concerned, however, that little information is available about consumer habits of self-medication with topical salves, ointments, creams, and powders, and, in particular, that the potential for misuse in acute and chronic skin conditions poses a problem. The Panel is also concerned about the possible use of inappropriate or harmful substances on skin wounds if safe OTC medications are not available for first-aid use.

Even though no information was submitted concerning the factors influencing the consumer's choice of a topical antibiotic, the Panel considered the following as possible factors:

(1) Physician availability or cost of physician visit;

(2) Media advertising such as in magazines, on the radio, or television;

(3) Suggestions from friends and acquaintances; and

(4) Satisfactory previous personal experience following advice of a physician or pharmacist.

Each of the above factors may lead to self-diagnosis and treatment that may not always be appropriate. One inappropriate use of a topical antibiotic preparation is prolonged application to a chronic, persistent skin lesion. This could produce skin sensitization and/or delay the consumer in obtaining more appropriate treatment. Another possible inappropriate use is the continued application of the antibiotic after a sensitization reaction has occurred. It is also possible that application of the antibiotic product over a broad area of the skin may alter the resident bacterial flora, leading to emergence of antibiotic-resistant strains of bacteria. Unfortunately, no data on consumer use of topical antibiotics are available from which to determine the relative importance of each of these concerns. Such data may not be relevant when topical antibiotics are used on minor cuts and wounds. However, the Panel concludes that product labeling must take into account, and attempt to eliminate, these problems.

The Panel is also concerned that the promotion of antibiotic products to physicians, for purposes other than those recommended for OTC use, may lead to confusion and misuse by the public. It is possible that the physician's use of topical antibiotics to treat certain skin infections may lead consumers to self-diagnosis of other skin conditions leading to treatment with inappropriate topical antibiotics. Labeling of the

topical antibiotics, for both OTC and prescription uses, should be designed to minimize this possibility.

The Panel considers that thorough, gentle cleansing of a minor skin wound to remove foreign material is the proper first step. The OTC antibiotic may then be applied to protect the wound or prevent infection, provided that benefit from its use has been demonstrated.

Suggestions were made to the Panel by Dr. Dillon (Ref. 1) that certain topical antibiotics might prove to be more useful in treating certain skin diseases than no treatment at all. Some skin diseases, such as impetigo and folliculitis, are recognized by the lay public as infections of the skin. The Panel agrees that such skin infections may be treated by the lay public with topical antibiotics if such have been proven to be effective.

REFERENCE

(1) Dillon, H., Transcript of open session of Antimicrobial II Panel, March 22, 1975.

E. EFFECTIVENESS OF TOPICAL ANTIBIOTICS

The OTC drug review regulations (21 CFR 330.10(a)(4)(ii)) contain the following definition of standards for effectiveness:

> Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. * * *

The Panel concludes that a "reasonable expectation * * * [of] clinically significant relief" has not been conclusively demonstrated for the OTC use of topical antibiotic products.

No data from well-controlled studies were presented to the Panel concerning either the therapeutic or prophylactic effects of OTC use of topical antibiotics on minor cuts, abrasions, or burns. The Panel concludes that no such data presently exist on the OTC use of these products.

In an effort to evaluate the clinical effectiveness of topical antibiotics, the Panel has relied on data generated by supervised use of topical antibiotics in hospitals and medical offices and by prescription use of topical antibiotics in outpatient home settings.

Most studies reviewed by the Panel dealt with professional medical treatment of acute skin infections, postoperative wound infections, and chronic skin diseases with secondary infections. While inferences concerning clinical effectiveness of topical antibiotics for OTC use on minor cuts, abrasions, and burns have been made from available studies (Ref. 1), the Panel concludes that such inferences may be unwarranted for the following reasons: The degree of wound contamination differs; the wounds differ in depth and amount of tissue destruction; the microorganisms likely to be introduced differ between hospital or office settings and "natural" settings; and patient characteristics differ with respect to hygiene, age, race, and ability to follow directions for product use.

1. Therapeutic effectiveness. Standards of medical practice regarding use of antibiotics in the treatment of skin infections have changed considerably during the past 30 years. In the 1940's and 1950's, when the topical antibiotics presently under review were developed and evaluated, many physicians were enthusiastic about their use in both the hospital and on an outpatient basis. However, reports from this period were largely of a testimonial nature, with no consistent attempt to document clinical diagonses, culture skin lesions, or demonstrate that formulated products with active ingredients were better in treating skin infections than their vehicles alone.

Because it is virtually impossible to look at a variety of skin lesions and assess exactly which bacteria are present, the Panel is unable to accept studies without cultures as proof of clinical effectiveness. The Panel is aware of the practical argument that cultures are time consuming and expensive, but concludes that such argument is not acceptable in studies purporting to demonstrate clinical effectiveness of topical antibiotic preparations.

The Panel has made a diligent effort to review all submitted material in order to arrive at its judgment concerning clinical effectiveness. It recognizes that honest differences of opinion may exist or the relative merits of different studies. The Panel also recognizes the inherent technical difficulties in attempting to scientifically document clinical effectiveness.

Many different dosage forms (i.e. creams, lotions, ointments, etc.) of these antibiotics are available, either as OTC or prescription, and it appears that there are relative differences in their effectiveness based upon the dosage forms used. It is a continuing concern of the Panel that many of the better designed studies (controlled) utilized an ointment vehicle for the antibiotic, and the results of these clinical studies show a lack of effectiveness in this vehicle. On the other hand, some studies (controlled and uncontrolled) suggested strongly that the antibiotics in solution or cream forms may have been effective in treating some skin conditions.

The Panel recommends OTC marketing of certain topical antibiotic formulations currently labelled as prescription products (primarily, cream formulations). This recommendation is based partly on theoretical considerations and partly on the effectiveness data discussed above. In any event, clinical studies with such dosage forms would still be required to establish effectiveness in the prevention and treatment of skin infections.

Since the early days of topical antibiotics, newer systemic antibiotics have largely replaced topical antibiotics for treating many skin infections. Several studies have shown that systemic antibiotics are superior to topical antibiotics in treatment of impetigo, with more rapid reduction of pathogenic bacteria from skin lesions and more rapid healing time (Refs. 2 through 7).

In addition, treatment of impetigo with systemic antibiotics rather than with topical antibiotics is accepted medical practice for prevention of possible glomerulonephritis (Refs. 2 through 7). Acute glomerulonephritis is a serious kidney disease that may follow streptococcal infections of either the skin or the throat (Refs. 8 and 9). While not all strains of streptococci are nephritogenic (capable of inducing nephritis), epidemics of nephritis may occur in populations exposed to impetigo caused by nephritogenic strains (Refs. 10 through 15). The risk of developing nephritis following impetigo caused by such a strain is significant, espectially in children less than 6 years of age (Refs. 16 through 19). Indigent children and children in warm, humid climates have a higher incidence of streptococcal sores and subsequent nephritis than children in colder climates. Although nephritis is predominantly a disease of children, adults may also be affected, especially in epidemic situations or following insect bites that become infected with nephritogenic streptococci (Refs. 20 and 21).

The Panel recognizes that the overall risk of developing nephritis following impetigo is not very great if patients are over 6 years of age and nephritogenic strains of streptococci are not prevalent (Refs. 22 and 23). There is concern that some children may develop nephritis because of lack of early treatment with systemic antibiotics. However, there is no conclusive proof at this time that treatment of streptococcal impetigo with topical or systemic antibiotics will prevent nephritis (Refs. 2, 8, 10, 13, and 24). Systemic treatment is presently preferred in cases of diagnosed impetigo because of more effective elimination of pathogenic streptococci from the skin.

The Panel is particularly concerned that indigent persons, unable to seek the treatment of choice (systemic antibiotics under proper medical supervision), may develop glomerulonephritis. In the Panel's opinion, this disease condition is extremely serious and may even be life threatening. The Panel believes that a significant population of indigent individuals exists in the United States who contact impetigo but seek no medical intervention and, therefore, risk developing glomerulonephritis. Although the use of topical antibiotics is not the treatment of choice for streptococcal impetigo, the potential risk is serious enough to suggest that this claim be seriously considered and evaluated as an added OTC indication for these products.

The Panel received communications from some organizations and individuals that presented their own recommendations on the safety and effectiveness of certain OTC topical antibiotics (Ref. 25). These recommendations were not supported with new or adequate data for objective evaluation. As a consequence of these comments, the Panel also met with a representative of the American Academy of Pediatrics and determined that the American Academy of Pediatrics' recommendations to the Panel were based on members' clinical

impressions rather than on a comprehensive review of the extensive data which was reviewed by the Panel (Ref. 26).

2. *Prophylactic effectiveness.* The Panel is concerned that little data from controlled studies have been submitted documenting clinical effectiveness of topical antibiotics for preventing infection in minor skin wounds such as cuts, abrasions, and burns. Most studies reviewed by the Panel dealt with professional medical treatment of diagnosed acute skin infections, postoperative wound infections, or chronic skin diseases with secondary infections. Prophylactic use of topical antibiotics has been reported in postoperative surgical wounds, on extensive burns, and with intravenous cutdown catheters. These reports suggest that prophylactic use of topically applied antibiotics may be efficacious in the prevention of wound infections following surgery, but do not permit any inferences concerning prophylactic effectiveness following minor cuts, wounds, and abrasions occurring outside the hospital setting. Furthermore, in some cases, formulations different from those currently marketed were tested, and in other cases conflicting results were obtained from these hospital studies. These reports do suggest that a controlled clinical trial of topically applied antibiotics in minor cuts, abrasions, or burns might be worthwhile to answer the question of prophylactic effectiveness.

In the opinion of the Panel, controlled clinical trials of topically applied antibiotics would not be as difficult as is often claimed. A prospective, randomized, double-blinded, controlled trial would have logistic difficulties, but is feasible. Of course, in any clinical trial, the group receiving a placebo should not be permitted to experience a deteriorating disease state, and the protocol should allow for active treatment intervention should this occur. The size of the groups needed in both the experimental and the control groups is dependent upon: (1) The expected difference between the experimental and control group (i.e., the probable effectiveness); (2) the expected incidence of the condition to be prevented—infected wounds cuts, burns, and abrasions; and (3) the chosen significance level and power of the statistical tests employed (Ref. 27).

Since it is thought that the incidence of such infections is low, this would enlarge the size of the groups required for entry into the trial. On the other hand, if the effectiveness (expected benefit or difference between treated and untreated groups) is high, this would correspondingly reduce the numbers required. It would be desirable to investigate the effectiveness of a heterogeneous group of infections such as small cuts, burns, and abrasions. This would still permit pooling of effectiveness data for these lesions as well as analysis by type of lesion (subgroup analysis).

The Panel believes that a single study of adequate size and design may provide sufficient evidence to make a judgment as to effectiveness.

3. Summary. The Panel finds an important deficiency in the data submitted concerning the effectiveness of topically applied antibiotics, i.e., the absence of randomized, prospective, double-blinded, controlled, clinical trials. Such trials would randomly allocate patients with cuts, wounds, burns, and abrasions to an experimental and a control group. The experimental group would receive the medication (for example, an ointment) with the active ingredients, and the control group would receive the vehicle (placebo) without the active ingredients. Neither the investigators nor subjects would know whether they were receiving active drug or placebo (a procedure called double-blinding). Both groups would be followed forward in time prospective design) and the incidence of infection ascertained.

The Panel is not willing to waive the requirement of double-blinded, controlled studies for clinical evaluation of topical antibiotic ingredients, despite the provision of the OTC drug review regulations pertaining to standards of effectiveness (21 CFR 330.10(a)(4)(ii) which states:

* * * Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.111(a)(5)(ii) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. * * *

The Panel concludes that a single, well-controlled study of adequate size and design may provide sufficient evidence to make a judgement of effectiveness.

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F. DRUG RELEASE FROM TOPICAL PREPARATIONS

The Panel reviewed data from several sources and heard a presentation from Robert Scheuplein, Ph. D., a recognized expert in the area of drug release from topical preparations. The vehicle currently employed most widely in topical antibiotic formulations for OTC sale is an ointment composed mainly of white petrolatum. White petrolatum is often formulated with other hydrophobic (insoluble in water) materials such as waxes or high molecular weight alcohols. In contrast to an ointment, a cream ve-

hicle is usually composed of a water miscible base such as an oil-in-water emulsion or a totally water-soluble base, such as the polyethylene glycols. The Panel is aware of other topically applied dosage forms for antibiotics, such as powders, but little data were provided on the bioavailability of the antibiotics from such dosage forms. It is essential to consider the influence of the vehicle on the effectiveness of a topical antibiotic preparation. The vehicle may be the controlling factor in the release of the active ingredient from the preparation. The following discussion attempts to clarify some of the problems facing the Panel in trying to assess drug release and the resulting effectiveness.

Drug release from any dosage form occurs at the interface between the vehicle and the tissue to which it is applied. The drug must leave the vehicle and enter the environment of the tissue before it can exert any biological activity. There are many factors that influence the rate and extent of this drug release. Some of these factors are: concentration of the drug in the vehicle; solubility of the drug in the vehicle; diffusion coefficient of the drug in the vehicle; partition coefficient of the drug between the vehicle and the tissue. Influencing each of these factors are other conditions such as the pH of the vehicle, drug or tissue; temperature; degree of hydration of skin, etc. Obviously, drug release from a dosage form is not merely a simple matter of smearing on a product and obtaining instantaneous results. Many physico-chemical interactions eventually determine success or failure of a product, apart from any activity of the antibiotic itself.

The Panel received limited data on release of certain antibiotics from the ointment dosage form. The ointment is the most widely used drug dosage form for OTC use at the present time, while the cream dosage form is almost exclusively limited to prescription sale. Some data presented to the Panel suggested that an ointment was better than a cream. Other data suggested that a cream was better than an ointment. The Panel concludes that inadequate research has been undertaken to design the most effective vehicle for a given topical antibiotic product. The Panel also is concerned that the existing OTC ointment dosage form may indeed be much less than ideal for the reasons discussed below.

It is recognized by the Panel that an occlusive vehicle (one that acts as a physical barrier), such as an ointment, has certain advantages in treating small wounds. Dr. Rovee pointed out that an occlusive dressing may aid wound healing (Reference 1). Dr. Scheuplein suggested that it was possible to formulate an ointment that would be as effective as a cream or vice-versa (Reference 2). Some of the effectiveness studies presented by the industrial representatives suggested that in some cases the ointment dosage form resulted in failures, while other studies reported success of treatment (Reference 3). Once again, conflicting data on drug release were presented to the Panel.

The Panel has determined that the topical antibiotics being reviewed are all water soluble with the exception of gramicidin, which is practically insoluble in water (Reference 4). These antibiotics exist in ointment dosage form as insoluble, suspended particles. From a physicochemical viewpoint, an insoluble particle in a fairly viscous, greasy vehicle would not be an ideal dosage form. If little or no diffusion through the vehicle takes place, then the only portion of antibiotic available for biologic activity is that which exists at the tissue interface at the time of application or that which then comes in contact from the receding boundary of the ointment (Reference 5). Perhaps it is for this reason that demonstration of effectiveness of antibiotic ointment has been difficult in some well-controlled studies.

In contrast, a cream dosage form has antibiotic in solution in the aqueous phase so that the antibiotic is more readily available for diffusion to the interface between the cream and tissue. In other words, a higher concentration of antibiotic can be made available to the tissue site over a short period of time from a cream formulation than from an ointment formulation.

The Panel is aware that in the early days of antibiotic formulation in topical products, technology to evaluate these dosage forms was not so sophisticated as it is at present. The Panel would urge a thorough study to determine all of the characteristics described above in light of the new technology to design a more favorable dosage form. If the cream or any other dosage form currently marketed for prescriptions use is determined to be both safe and effective, consideration should be given to marketing these dosage forms OTC.

The release of drugs from various vehicles has been the subject of many reviews and research papers. Consistently, these papers indicate that a formulation or vehicle for a given chemical must be specifically designed for that chemical to obtain maximum drug release. In formulating a cream or ointment, the physical properties of the drug and vehicle must be balanced in such a way as to provide optimum release. Specific additives may enhance or retard release of a chemical from the vehicle. Gandhji and Mithal (Reference 6) have shown that by simply incorporating a surfactant, release of chloramphenicol and tetracycline from an ointment formulation was enhanced. It appears to be the Panel that proper formulation of vehicles for the various antibiotics, based on such current information, could very likely result in significant improvement in antibiotic effectiveness.

A recent review of the broad problem of release of drugs from topically applied dosage forms has been published by Grasso and Lansdown (Reference 7). The Panel also studied the reviews by Poulsen (Reference 8), Katz and Poulsen (Reference 9), and Idson (Reference 5). These comprehensive reports focus on percutaneous absorption, but the basic problem of drug release from topical preparations is also discussed. The discussion above is not intended to be an exhaustive summary of these reviews, but it does form the basis for the recommendation presented in this report.

The Panel is certain that manufacturers of topical antibiotic ointments are aware of the voluminous literature concerning percutaneous absorption of drugs, influence of a vehicle on the release of drugs, and physiological factors influencing release of drugs (high or low sebum content, or denuded verus intact skin). The Panel believes that the previous arbitrary distinction between OTC and prescription topical antibiotic products is not rational. It strongly urges testing of other topical dosage forms (gels, solutions, creams, lotions) for possible OTC use. However, such testing should take into consideration the pharmacokinetic factors discussed above.

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G. WOUND HEALING

Wound healing may be altered by excessive bacterial growth in the damaged tissues (Ref. 1). The manufacturers state that topical antibiotics speed wound healing, presumably by reducing bacterial growth. It is recognized that these terms (such as "speeds healing", or other similar terms) are meant to imply that by reducing excessive bacterial growth in a wound, normal healing is enhanced. It also implies that large numbers of bacteria, or their products in a wound, slow or impede wound healing. There are no good data to indicate that the normal healing time of a clean wound can be altered by an antibiotic cream or ointment. Scientific evidence currently available to the Panel does not sufficiently answer the question of the role of bacteria in minor skin wounds in the normal individual. There is little evidence to support the claims that reduction of the number of bacteria in wounds will shorten dermal and epithelial healing times.

Wound repair rates may vary depending on the number and types of bacteria or their metabolites present in the wound. Some wounds do not heal normally in the presence of some bacteria or bacterial metabolites as demonstrated by Rovee (Ref. 1).

Several studies in the past 10 years have demonstrated the influence of the local wound environment on wound healing in the skin. One of the important variables in epidermal wound healing is the amount of moisture or degree of hydration of the skin. Several investigators have shown that maintaining tissue hydration by the application of plastic film, or other slightly less occlusive dressings, increases epithelial migration and shortens the time necessary for the epidermis to cover the wound when compared with open wounds (Refs. 2 through 5). It appears that ointments that are semiocclusive might also enhance epidermal repair by creating a moist environment in the wound. Whether or not this actually occurs could not be determined from that data submitted.

The panel concludes that the role of an antibiotic ointment in wound repair is still largely unknown.

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H. ANIMAL AND HUMAN MODELS

The study of experimental infections in humans is often impossible, impractical, or dangerous. Therefore, various animal and human models have been developed to study the infection process. Information that can be obtained from models is often useful, particularly in regard to: (1) obtaining information that cannot be derived ethically or practically from clinical trials; (2) predicting appropriate dosage levels for desired responses in clinical trials; (3) determining toxicologic hazards; and (4) performing controlled studies on adequate numbers of subjects to enable significant statistical analysis.

Controlled clinical trials to determine the therapeutic and prophylactic effectiveness of topical antibiotic agents may be difficult for the following reasons: ethical considerations; large size of the study required; cost; logistics; time commitment; and difficulty in patient compliance. Although models have been used historically to determine clinical effectiveness, a careful analysis of limitations associated with models must be made. There are great difficulties involved in drawing inferences from animal models and applying conclusions to human populations. It is necessary to validate model systems and demonstrate that they have predictive ability for human clinical conditions.

In dealing with the use of models of the infection of minor wounds, burns, and abrasions, the differences and similarities of a specific model to the normal infection process can be examined.

1. *Normal human infection process.* a. Streptococci and/or staphylococci occur on the skin at the time of injury, or are often carried there or transmitted from an infected source, such as a biting insect.

b. A lesion occurs on the skin.

c. The lesion provides the environmental situation required to allow the organisms that are present, or have been applied as the lesion is made, to reproduce and invade.

d. An infected lesion results.

e. The organisms causing the infection are present at the time of injury.

2. *Human model as described by Kligman and Marples.* a. The lesion is artificially made on the skin. Time is allowed for healing of the lesion (24 hours).

b. Pathogenic staphylococcal organisms are added to the lesion and allowed to remain for 6 hours before application of antibiotic agents.

c. In some testing situations, the normally occurring flora are allowed to expand for varying times, producing the successive replacement populations before the antibiotic is applied. In some instances, the antibiotic is added after 24-hour healing of the lesion to prevent expansion of the flora (Refs. 1 and 2).

3. *Differences and similarities between natural and induced skin infection.* a. In the natural human infection, there is often a mixed population of pathogens; in the model, only staphylococci or coliforms have been used since the streptococci would be a risk to the subjects.

b. In the model, since there will be residual antibiotic, attempts must be made to neutralize the residual agent.

c. In the model system, the organisms against which the antibiotic is acting are often the normal skin flora consisting of coagulase-negative staphylococci, diphtheroids, and some gram-negatives. In the natural infection, in addition to the normal skin flora, other organisms (from exogenous sources) will likely be the infecting agents. These agents are the specific target of the applied antibiotic.

d. In the model system, organisms and active formulations may be inadvertently transmitted from one lesion to another, since artificially produced lesions may be made at close intervals on the forearm.

4. *Animal models for skin infection.* Several animal models have been used to demonstrate the therapeutic and prophylactic effectiveness of topical antibiotics. In an extensive review of such animal models, Miller (Ref. 3) describes some of these models, including: the production of abscesses in inoculated suture stitches in rats and guinea pigs; a rabbit ear-wound model; infection in inoculated and depilated rat skin; surgical wounds in the rat; a burn model inoculated with *Pseudomonas* in the rat. In addition to rats, guinea pigs, and rabbits, other test animals have included hamsters, mice, dogs, and goats (Refs. 4 through 18). Mice and rats are apparently not particularly good test animals, due to their general resistance to superficial infections.

Work with these animals has not been standardized, and has included a variety of topical antibiotics, dosage forms, experimental techniques, and experimental models. Antibiotic creams, powders, ointments, sprays and solutions have each been tested in only a few of the models. The Panel concludes that no generalizations about effectiveness of topical antibiotics can be made from currently available animal model data.

The Panel also concluded that, of all the animal models reviewed, the impetigo model in hamsters and the wound infection models in guinea pigs appear to be the most promising for testing some aspects of effectiveness of topical antibiotics for OTC use. In the hamster model, impetigo is induced by injecting cultures of *Staphylococcus aureus* or hemolytic streptococci into the dermal layer of the skin (Refs. 4 through 6). This is the only animal model known to the Panel that produces a superficial bacterial infection similar to naturally acquired impetigo in humans. In guinea pigs, wound infections have been produced by inoculating various types of bacteria into surgical incisions in the dorsal interscapular regions (Refs. 7 through 11). The guinea pig wound infection model appears to mimic superficial wound infections in humans (Ref. 9).

The Panel encourages further development of other animal models that may be useful in evaluating topical antibiotics.

5. *Human models for skin infection.* Some studies with human models involve normal skin. Many investigators have observed that normal human skin is very difficult to infect (Ref. 19). Since 1959, numerous investigators have searched for a method that will consistently produce superficial skin infection in humans (Ref. 20). Application of 5 million pathogenic microrganisms to normal intact skin or intact skin previously exposed to ultraviolent light, high humidity, cutting oils, or crude coal tar have failed to induce infection, even when the skin was tightly occluded with polyethylene wrap which favors proliferation of bacteria (Ref. 20). Intradermal injection of pathogenic organisms will also usually fail to induce infection (Ref. 20).

Disruption of the uppermost layers of the skin (stratum corneum and epidermis) through physical or chemical trauma seems to be a necessary prerequisite for producing skin infection in human skin. Many methods of producing trauma have been tried, including sandpapering, scraping with a scalpel, abrasive scrubbing with a pot cleaner, hair plucking, puncturing with a blood lancet, sequential stripping with cellophane tape, and production of blisters with cantharidin or ammonium hydroxide (Refs. 19 through 22). While a physical break in the skin is necessary to establish skin infection, it is obviously not the only factor necessary since many of the above

techniques have failed to consistently produce infection. Search is still underway to create a model in which a small number of pathogenic organisms will multiply and consistently produce clinical infection (Ref. 21).

In 1970 it was reported that some regions of human skin, particularly the legs, are easier to infect than other regions such as the arms or back. These differences are possibly due to circulatory changes (Ref. 19). The technique used involved stabbing the skin with a blood lancet that contained a drop of pathogenic inoculum of staphylococci or streptococci followed by occlusion of the skin with plastic tape. Superficial infection could be induced 38 percent of the time on the legs but only 15 percent of the time on the back and 13 percent of the time on the arms. Attainment of a 38 percent infection rate on the legs was considered to be highly successful in comparison to that obtained in earlier studies.

In 1972 a human model for superficial infection with *Staphylococcus aureus* was reported by Marples and Kligman using the technique of stripping superficial layers of the skin with cellophane prior to inoculation of organisms (Ref. 21). Repeated stripping removed the stratum corneum completely, revealing a moist glistening surface. A rest period of 24 hours was then allowed, to enable the skin to reestablish some barrier and to prevent bacteria from entering the blood stream. Following this period, staphylococci were applied and the region occluded with plastic film for 24 hours. A bright red, tender, moist area with serosanguineous (blood-tinged) exudate resulted. Simulation of a wound in this way was thought to produce several conditions favoring rapid proliferation of microorganisms: moisture, serum for nutrient, protection from white blood cells by the underlying intact epidermis, and removal of competing microorganisms present in the superficial stratum corneum of the normal skin (Ref. 21). When this model is used, the flora of the skin changes after the occlusive wrap is applied to a lesion. The model could well be used to compare antibiotic agents. However, effectiveness must necessarily be demonstrated in clinical trials because this model system uses normal skin bacteria to demonstrate the activity of the antibiotic. Something more is necessary to make pathogens grow on normal skin than is required to make normal skin bacteria grow (Ref. 23).

The type and number of organisms developing successively after the hydrating occlusive wrap is applied generally proceeds as follows: The coagulase-negative staphylococci grow in the first 48 hours expanding from 10^8 to 10^7 per square cm; by 1 week, the flora has become predominately diphtheroids. Some gram-negatives occur at the end of 1 week but do not usually predominate.

6. *Uses of the human model.* The human model has been used in several ways to study antimicrobial agents such as:

a. *Expanded flora test.* The test can evaluate broad spectrum antibiotic activity against large numbers of both gram-positive and gram-negative organisms induced by pretreatment occlusion. The expansion of flora that normally occurs when an occlusive wrap is applied to the skin is inhibited. This test differs from the occlusion test only in that plastic wrap is applied for 48 hours prior to application of antibiotic solutions. To be considered effective, a test material must destroy 99 percent of microorganisms. Bacterial counts will be consistently low only if the antibiotic is active against both gram-positive and gram-negative organisms. Only bacitracin and chloramphenicol were found to be effective at the 0.01 percent concentration level, while neomycin was effective at 0.1 percent and chlortetracycline was effective at 1.0 percent concentrations (Ref. 22).

b. *Occlusion test.* The test primarily estimates the bacteriostatic activity of an antibiotic against gram-positive microorganisms found on normal skin, showing how well the agent prevents a small number of bacteria from rapidly proliferating. Lesions are produced either by stripping with cellophane tape or by application of ammonium hydroxide, followed by inoculation with pathogenic organisms (usually staphylococci) and then covered with occlusive wrap. Lesions may be treated with a test compound after inoculation, and then inhibition of growth is observed or rapidity of healing is judged. In this test, solutions of antibiotics in water or alcohol were applied to 5-cm skin squares which were then occluded for 48 hours. Bacitracin, neomycin, and chloramphenicol were found to be markedly inhibiting at the 0.01 percent concentration (Ref. 22).

c. *Persistence test.* The test determines the reservoir effect of the antibiotic, or its ability to bind to the stratum corneum to give a prolonged effect (Ref. 22). In this test, 1 percent solutions of antibiotics were applied 3 times daily for 3 days to a 5-cm square on the forearm. After 3 days, these areas were occluded for 24 hours and then sampled for bacteria. Occlusion allows bacterial growth in the presence of the specific antibiotic being tested. The persistence of antimicrobial activity after application on the skin extends the time over which an antibiotic can exert an effect on a bacterial cell. This test is one means of measuring this characteristic in a human model.

d. *Reduction of expanded flora produced by occlusive wrapping of the site.* The inhibition of the expanded flora can be observed by application of antibiotics after sufficient time period of occlusion with the wrap. Prevention of expansion of the flora can also be used to test antibiotic activity. Antibiotic is applied to the wound or test site, and after continued occlusion, the inhibition of expansion of the flora is observed (Ref. 21). A cream containing neomycin and gramicidin was found to have eliminated staphylococci from most lesions when cultures of lesions were done 18 hours after the antibiotics was applied. Similar studies using this model have been performed with polymyxin, bacitracin, and a mixture of polymyxin and bacitracin showing that the combination polymyxin-bacitracin ointment was much more effective than either ingredient alone in preventing infections with mixed inoculum containing *Staphylococcus aureaus* and *Escherichia coli* (Ref. 24). A similar model, in which the stratum corneum was removed by producing blisters with ammonium hydroxide rather than by stripping, was described to the Panel (Ref. 24).

The method has been applied to the preliminary testing of topical antibiotics for prophylaxis, using the intact human skin of the forearm (Ref. 22). The forearm was wrapped with occlusive plastic film for 48 hours either before, during, or following application of topical antibiotic to determine the ability of the antibiotic to supress bacterial proliferation stimulated by the moist, warm environment of occlusion. Various concentrations of antibiotics were used, including 0.01, 0.1, and 1.0 percent concentrations of bacitracin, neomycin, chloramphenicol, and chlortetracycline. Immediately after removal of the plastic film, bacterial sampling of test areas was performed using the cup-scrubbing method with a detergent scrub to facilitate sampling.

To be useful and to draw valid conclusions, the similarities and dissimilarities of this or any model to the human infection must be examined.

7. *Summary.* The Panel believes that the results of studies with both animal and human models can serve useful and important purposes. However, they have also concluded that careful attention should be paid to the variables that may dramatically influence the results and therefore their applicability to clinical conclusions.

a. *Animal models.* Review of the current literature suggests, and the Panel concurs, that hamsters and guinea pigs are satisfactory experimental animals in which to consistently produce skin infection. The models discussed above appear to provide reliable test systems for evaluating both therapeutic and prophylactic effectiveness of topical antibiotics. Care must be taken, however, in comparing test results obtained in different species.

The Panel recommends that attempts be made to standardize the following variables in animal models:

(1) Location of contaminated wounds.
(2) Depth of incision.
(3) Type and quantity of inoculum.
(4) Method of inoculation.
(5) Time between inoculation and treatment.
(6) Method of culturing.
(7) Technique of treatment.
(8) Method of wound closure.
(9) System of grading infections.

The above are suggestions that should be considered. See sections under individual antibiotics and/or combinations thereof for required testing described elsewhere in this document.

In working with prophylactic surgical wound models, effort should also be made to avoid leaving necrotic tissue, foreign bodies, dead space, or hematomas that might interfere with wound healing.

b. *Human models for treatment and prophylaxis.* Review of the current literature and of unpublished data presented to the Panel leads the Panel to believe that a few satisfactory and safe model systems presently exist for producing experimental superficial infection in human skin. Successful models require disruption of the uppermost layers of the skin through either cellophane tape stripping or ammonium hydroxide blister formation.

Prophylactic effectiveness can also be evaluated using the same model by inserting a topical antibiotic into the test system between the time of bacterial inoculation and the usual appearance of clinical lesions.

A second model for testing prophylactic effectiveness includes the use of plastic wrap occlusion on normal forearm skin to induce bacterial proliferation. Application of various concentrations of antibiotic before, during, or after occlusion helps indicate the bacteriostatic and bactericidal effectiveness of a test product against both gram-positive and gram-negative microorganisms.

The Panel recognizes that no single test system can possibly encompass all therapeutic and prophylatic applications for which OTC topical antibotics are designed. Separate protocols will have to be designed to consider such variables as antibacterial spectrum and duration of antibiotic action. The Panel concludes, however, that existing or comparable model test systems in humans might be utilized in such a way that they will help to screen and validate the effectiveness of those antibiotic agents that might usefully be further tested in clinical studies.

c. *Clinical studies.* The final appraisal of topical antibiotic effectiveness must take place in a clinical setting under circumstances conforming as closely as feasible to actual circumstances in the community, and must adhere to accepted ethical standards. Animal and human models may lessen the need for extensive, time-consuming, expensive clinical trials on agents that are found to be ineffectve in the model system. The Panel expects that, at a minimum, adequate clinical studies would be conducted to confirm and validate the results of model studies (if performed). For example, a small, closed population could probably be found in which the infection rate of small wounds could be determined. With adequate controls and experimental design, it could then be demonstrated whether the application of a topical antibiotic alters the normal infection rate.

A variety of strategies is available to limit the number of subjects in these clinical studies, including sequential designs and use of artificially induced wounds in volunteers (Ref. 25). It is suggested that prophylactic clinical trails in humans not be initiated unless there is sufficient evidence to suggest that they will show a beneficial effect from the tested products.

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I. SAFETY OF TOPICAL ANTIBIOTICS

1. *Rationale for determination of safety factors.* Data necessary to fully assess either benefit or risk were not provided to the Panel. However, with the possible exception of neomycin, the Panel believes topical antibiotics would provide a minimal risk to the user when applied to small wounds. The Panel is aware that these preparations are intended by the manufacturer for use on small cuts, burns, and abrasions. If use in actual practice were restricted to such application, the risk from application of topical antibiotics would be minimal. However, the Panel is concerned about the misuse of OTC topical antibiotics, such as application to diaper rashes, extensive heat rashes, burns, and stasis ulcers. The absorption of significant amounts of antibiotics from certain formulations on large burns is known to occur (Ref. 1). Misuse of these products increases the risk to the patient.

Even if one assumes the risk is small, the assessment of benefit of the submitted topical antibiotic preparations is a difficult task. The Panel recognizes that topical antibiotics are often used for treatment, rather than prevention, of infection by the lay public. Therefore, the Panel divided its assessment of benefit into two categories of use: prophylactic and therapeutic.

In considering the concept of a benefit-to-risk judgment, the Panel discussed safety factors as a desirable means of arriving at an assessment of the risk. In general, the Panel endorses the statement on safety factors for topically applied antimicrobial agents as recommended by the OTC Antimicrobial I Drug Review Panel published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33112). This proposal recommends a 100-fold safety factor in the applied dose.

The Panel considered the problem of testing the safety of topical preparations in animals and extrapolating the results to human use. It is difficult to obtain comparable absorption characteristics or tissue drug levels from topical studies

in animals and man. The use of the blood level of the drug or its metabolite(s) may simplify this evaluation. Toxic responses can be obtained by systemic dosing that produces relatively high blood levels. If necessary, the range of blood levels produced after topical application should be determined experimentally in man and animal. The Panel expects that in most cases the lowest drug or metabolite blood level and the highest blood level found after topical application will differ and thus help establish the safety of the product.

Blood levels of antibiotics in animals can be used in the overall evaluations of "effect levels" (lowest dose that produces a toxic effect) /"no-effect levels" (highest dose that produces no toxic effect). The effect/no-effect dose levels are the result of several interrelated mechanisms: (1) absorption rate from the site of application, (2) metabolism by enzymes, (3) distribution and storage in the tissues and (4) excretion.

The Panel has concluded that it is imperative to determine safety factors from the "effect" and "no-effect" blood levels in appropriate species of animals. This may be done by direct administration of antibiotics into the blood where feasible, or by determination of blood levels after administration by another route. Following such a direct determination, blood levels after topical application should be determined in order to assess absorption factors and rates, metabolism rates, and excretion rates in case there are wide variations between topical absorption and absorption from other routes of administration in animals.

Extrapolation of the animal safety data into realistic terms for determining safe human use is one of the most complex and inexact procedures. One purpose in obtaining animal safety data is to determine the lowest concentration causing toxic effects. Studies should be conducted to determine the highest blood levels achievable in man from maximum exposure to topical application. If the blood level in man is significantly less than the toxic levels in animals, the antibiotic product may be judged safe. The Panel recognizes that the term "significantly less than the toxic blood level" is not definitive, but a meaningful, numerical factor cannot be assigned for an antibiotic or any other chemical until a complete toxicological profile has been established for that chemical. There are many factors that go into a toxicological response to a chemical that may prevent adequate definition of "significant", including metabolic rates, whether damage to a tissue is cumulative, repair rates of any damage, rate of exposure, and others. Therefore, the Panel would only recommend that the blood level of an antibiotic be significantly less than the toxic blood level and, at the time the judgment is made, all available factors be used to assess the significance in the difference in blood level.

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2. *Additional safety factors.* It is recognized that in some cases the blood concentrations resulting from short term topical application of a product may be far less than that which produces overt toxicity. However, blood levels are affected both by concentration and length of exposure. Therefore, all that is needed is a study that will clearly define the order of magnitude of the differences in blood levels and durations of exposure.

In those cases where there appears to be a problem, as for example, neomycin, the following tests would be recommended: appropriate dose response studies in animals, designed to determine the lowest blood level and minimum duration of exposure to an antibiotic that will cause a toxic reaction. These studies should determine both the LD_{50} and slope characteristics of a dose response curve for the most sensitive toxic effect. Parenteral administration of the antibiotic is appropriate for these studies. Both the release of the antibiotic from the topical formulation proposed, and the amount absorbed, should be determined in animals and humans.

From the tests mentioned above, the "effect levels" (lowest dose that produces a toxic effect) and the "no-effect levels" (highest dose that produces no toxic effect) in animals, can be determined as well as the blood level associated with normal human exposure. Comparison of these values allows estimation of any potential risk.

In vitro susceptibility testing. When an antibiotic is prescribed for parenteral or oral administration, a clinical specimen, e.g., urine, blood, or other specimen is taken and cultured to isolate bacteria and perform a series of susceptibility tests to determine what antibiotic is appropriate. As the use of topical antibiotics has developed, attempts to cover most types of organisms that may cause topical or superficial infections have been made. Frequently, this is done by combining more than one antibiotic in a formulation. As a consequence, when a topical infection is diagnosed, the assumption is made that one of the antibiotics is active against the infecting organism. The result of this procedure is that cultures and susceptibility testing are rarely done by the clinician. However, adequate testing procedures are necessary if controlled clinical studies are performed. One essential requisite of a controlled study of topically applied antibiotics is the proper performance of susceptibility testing.

In vitro susceptibility testing of clinical isolates from infected tissues to antibiotics is commonly performed on specimens from systemic infections and more rarely on specimens from superficial or topical infections.

This testing procedure most often determines, in a tube of liquid agar medium or an agar plate, whether the organism from the site of infection (clinical isolate) is susceptible to (can be killed or inhibited by) the concentration of antibiotic that is found in the blood or in the specific tissue being treated. after administration of the dose of the antibiotic drug. Organisms that are not susceptible to this specified concentration are said to be resistant.

As it became obvious that some organisms were resistant or became resistant to antibiotics, mechanisms for determining the degree of resistance were developed. The basic procedure is to use a standardized inoculum against serial dilutions of the antibiotic. This is often time-consuming so it has been simplified by using a standardized inoculum seeded on the petri plate onto which is placed a paper disc containing a specific quantity of antibiotic. A specific zone diameter measured on the plate can be used as a predictor of the minimal inhibitory concentration.

As the procedures for performing susceptibility tests were widely adopted, both the dilution and the disc procedures were increasingly used to predict susceptibility to specific antibiotics. As the number of antibiotics to be tested expanded greatly, not only did the number of discs greatly increase, but in some cases, both high and low content discs were used.

As a result of several collaborative studies, to avoid the confusion of previous methods, a uniform disc procedure was adopted. This currently accepted procedure is referred to as the Official Susceptibility Testing Procedure and is identified in the regulations as the certification procedure for antibiotic sensitivity discs (21 CFR 460.1).

The central concept of this proposal is that only one disc is chosen to represent, and therefore predict, the susceptibility of a specific isolate to a family of antibiotics. The selection of the specific disc and content of antibiotic was carefully done and was based on large amounts of computer-generated data.

The Panel has recognized that cultures are not routinely taken, identified, or tested for susceptibility in superficial infections. If they are performed, the Panel concludes that the official susceptibility testing procedure mentioned above should be utilized.

The Panel also recognizes that other procedures—including automated tube dilution (serial) determination of minimal inhibitory concentrations, the use of laser beams, or use of radioactive substrates—are being developed for susceptibility testing.

3. *Incidence of complaints.* It has been argued that because of the low incidence of consumer complaints, it can be concluded that OTC topical antibiotics are safe and effective. Consumer complaints reaching pharmaceutical manufacturers concerning adverse reactions or lack of effectiveness of a product are often col-

lected and studied. The number of such complaints, compared to the total number of product units sold, is reported as a ratio of adverse reactions per million product units sold. Industry traditionally regards the "incidence" of complaints as a sensitive index of both product safety and consumer acceptance of a product. If complaints about a product become too numerous, the product may be withdrawn from the market.

However, although adverse reactions voluntarily reported to manufacturers have some utility, they suffer from the following deficiencies:

a. The actual number of adverse drug reactions occurring is not known, i.e., the amount not reported is not available.

b. It is not always clear if the reaction is linked to the agent by the user, particularly if the reaction is delayed or unusual.

c. Persons may not be motivated to write letters of complaint, or may not know where to write.

d. No central registry combining reports of all manufacturers has been established.

e. In addition to incomplete ascertainment of the incidence of complaints, there is also lack of knowledge of the size of the population at risk, which often can only be estimated using sales data.

f. Validation of the reports is usually not carried out.

Nevertheless, serious and very frequent adverse drug reactions may be recognized by these systems although accurate quantification by means of incidence rates is impossible.

For topical antibiotics, the overall "incidence" of adverse reaction complaints recieved by industry is extremely low, calculated to be 0.68 per million units sold, with variation between products of 0.11 to 1.75 per million. The overall incidence of complaints concerning lack of effectiveness is 0.12 per million, ranging from 0.07 to 0.28 per million. Most complaints have referred to a "stinging" or "irritation." Poison control statistics for the years 1968–1973 have revealed 1,841 inquiries per year concerning ingestion of topical antibiotic products by children, with no serious injury or need of hospitalization (Ref. 1). Although pharmaceutical manufacturers realize that not all consumer complaints are reported, they still consider topical antibiotics to have a remarkably good record of safety and effectiveness.

However, the Panel suspects that most consumers and physicians do not take either the time or effort to report adverse reactions or treatment failures from OTC drug products to the manufacturers.

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J. LABELING OF OTC TOPICAL ANTIBIOTIC PRODUCTS

The Panel reviewed the general and specific labeling requirements previously adopted by FDA for OTC topical antibiotic preparations (21 CFR 369.20). These requirements provide for labeling information concerning the identity of ingredients, directions for use, and general and specific warnings. The Panel concurs that these requirements are appropriate for OTC topical antibiotic preparations and the labeling is discussed below.

After review of all labels of OTC topical antibiotic preparations submitted, the Panel recommends the following:

1. *Indications.* The indications for use of a topical antibiotic preparation should be simple and clearly stated. If the product is used for specific indications, such as first-aid in small superficial skin wounds including cuts, abrasions, and burns, the label should so state. The directions for use should provide the user with a reasonable expectation of the results anticipated from use of the product. Statements of indications for use should be specific and confined to the conditions the product is recommended for, such as small and superficial skin wounds, cuts, or abrasions. No reference should be made, or implied, regarding the alleviation or relief of symptoms unrelated to the indication (condition) for use of the product, e.g., hand eczema, leg ulcers, diaper rash, and extensive burns.

Effectiveness must be defined without vague or unsupported claims. Phrasing that promises general benefits such as improved healing, or warns against the hazards of superficial skin wounds, is unproven and thus unacceptable. Undocumented claims that topical antibiotics aid or hasten healing are not supported by present scientific evidence and thus are not acceptable.

The Panel recognizes that certain treatment claims for skin wound antibiotics may be proposed for labeling, following completion of studies to establish prophylactic and therapeutic effectiveness. One such conceivable claim would be "for the prevention and treatment of impetigo." The Panel concludes that such a claim would be acceptable, but only after the effectiveness of a topical antibiotic for this claim has been conclusively established in controlled, double-blinded studies, as outlined elsewhere in this document.

2. *Ingredients.* Topical antibiotic products should contain only active ingredient(s), plus such inactive ingredients as are necessary for formulation. While the label should state in metric units the quantity of each active ingredient, this is not always a simple task with topical antibiotics. References are made in this document to activity or potency in terms of units and micrograms (mcg). The activity assigned to each unit or mcg is equivalent to an International Unit if such has been defined by the World Health Organization. The units of potency set forth in the United States Pharmacopeia, except in a few instances, are identical to the International Units. The terms applied to the antibiotics reviewed in this document, as to the activity (potency) assigned or contained in a specific amount of a standard, are defined in the discussion of specific antibiotics. In some cases, the FDA units have been equivalent to an International Unit for the same antibiotic and in others, not. Both bacitracin and polymyxin B are defined in terms of units, while most other antibiotics are defined in terms of micrograms.

The Panel strongly recommends that all inactive ingredients be listed since the consumer may need this information for a variety of reasons. However, the product should not be promoted for therapeutic claims on the basis of its inactive ingredients. The label should indicate which ingredients are the inactive ones.

3. *Directions for use.* The label should read: "After gentle washing, apply a small amount (an amount equal to the surface area of the tip of a finger) directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily."

4. *Warnings.* The Panel has reviewed the current regulation (21 CFR 369.20) regarding labeling of antibiotics for external use for prevention of infection which states:

Caution—In case of deep or puncture wounds or serious burns consult physician. If redness, irritation, swelling, or pain persists or increases or if infection occurs, discontinue use and consult physician. Do not use in the eyes.

The use of topical antibiotic preparations "in deep puncture wounds" is of special concern to the Panel. Therefore, the Panel endorses this warning and the prohibition of use. The reason for this is that it is extremely difficult to place the antibiotic into the recesses of such a wound. In fact, it would be strictly a topical application and the patient may be lulled into a false sense of security. Additionally, the Panel strongly recommends that deep puncture wounds should be treated by a physician so that adequate protection against tetanus may be achieved.

Labels of topical antibiotic preparations should also specifically state:

a. "Do not use on long-standing skin conditions such as leg ulcers, diaper rash or hand eczema."

b. "If itching, redness, swelling, or pain develops or increases, it may be a sign of infection or alergy. Stop use and see a physician." To avoid redundancy, this phrase may be merged with the broader caution set forth above under item a.

c. "Do not use longer than 1 week."

The reason for this last recommendation is that most small, superficial skin wounds including burns, cuts, and abrasions will heal almost completely within 1 week. The Panel is concerned that continued use of a topical antibiotic preparation on an unhealed lesion may delay diagnosis and treatment of a more serious skin disease, e.g., a spreading deep bacterial infection, or a wound contaminated with foreign debris such as glass.

5. *Category II labeling.* The Panel concludes that the use of some labeling claims are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The following phrases are misleading and confusing to the consumer and unacceptable for labeling of skin wound protectants and antibiotics for skin wound treatment:

a. *"Helps kill bacteria."* Unless determination of the antibacterial properties of the specific antibiotic are made with obective in vitro or in vivo testing, claims of activity must not be made. Qualification of whether the activity is helped or not is misleading.

b. *"Is not an uncommon sensitizer."* The Panel believes the phraseology used in the above claim is extremely confusing. Due to the use of a double negative, the average consumer could possibly interpret this statement to mean a drug that commonly sensitizes or, conversely, one that never sensitizes.

Since the intent of this Panel is to assure clarity in the meaning of these claims and since the phrase mentioned above is confusing and vague, the above claim will be considered misleading.

c. *"Antiseptic."* Within the scientific community, and also as set forth and published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33114), the term "antiseptic" is defined. These are often synthetic chemicals, often used in fairly high concentration, which have antimicrobial activity and in use prevent infection. In contrast, an antibiotic is defined as a chemical derived from a microorganism that has antimicrobial activity in low concentrations and may be used to prevent or treat infection. The Panel is concerned, as it attempts to set standards in this area, that terms and claims not be ambiguous or have dual meanings. This is the case with the term antiseptic, which should refer only to synthetic chemicals and should not be used to refer to antibiotics.

d. *"Aids, speeds, helps, augments, or hastens healing" (or any term or phrase that suggests that there can be decreased healing time from application of an antibiotic-containing product on various cuts, wounds, or abrasions).* These claims imply to the consumer that antibacterial products may play a primary role in the healing process and can shorten healing time. However, they generally act only to remove high numbers of pathogenic microorganisms from the wound that might slow the healing process. This action allows the body's healing processes to follow their normal course. Probably no ingredients reviewed directly improve healing as the claims imply; therefore, the Panel concludes these or similar phrases are not only false but also misleading.

6. *Classification of topical antibiotics.* The Panel reviewed all active ingredients that were the subject of submissions made to the Panel pursuant to the standards for safety, effectiveness, and truthful labeling set out in the OTC drug review regulations (21 CFR 330.10).

In accordance with the regulations, the Panel's findings with respect to these ingredients are set forth in three categories:

Category I. Conditions under which topical antibiotic products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which topical antibiotic products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The following classification of topical antibiotic ingredients as skin wound protectants or skin wound antibiotic preparations (see table below) was developed by the Panel in an attempt to simplify categorization of ingredients and eliminate labeling confusion:

Summary of findings for topical antibiotics—Categorization

Antibiotic ingredient (used alone)	Skin wound protectant	Skin wound antibiotics	Susceptible bacteria
Bacitracin	I	III	Gram-positive.
Gramicidin [1]	III	III	Do.
Neomycin [2]	III	III	Gram-positive and some gram-negative.
Polymyxin [3]	I	III	Gram-negative.
Tetracyclines.	I	III	Gram-positive and some gram-negative.

[1] Toxicological data are insufficient to permit final classification.
[2] Sensitization data are insufficient to permit final classification.
[3] Only to be allowed in combination products containing other antibiotics since, when used alone, may provide selective growth of gram-positive bacteria.

III. SKIN WOUND PROTECTANTS

A. GENERAL DISCUSSION

The Panel has determined that a given antibiotic ingredient may be in Category I for one set of conditions or label claims and in Category III for another set of conditions or label claims.

The antibiotics specified as Category I for use as a skin wound protectant are generally recognized to be safe and effective for this use. A skin wound protectant is a safe, nonirritating preparation applied to small cleansed wounds which provides a protective physical barrier, conforming to the barrier testing for skin wound protectants described in the FEDERAL REGISTER of September 13, 1974 (39 FR 33140), and may also include a chemical (antibiotic), which neither delays healing nor favors the growth of microorganisms. For example, the Panel visualizes that a skin wound should be gently cleansed as the initial treatment by the patient as soon after the wound occurs as possible. Following this, an antibiotic preparation in ointment form may be placed on the wound to prevent contamination with extraneous matter, including bacteria. The action of the preparation is one of a physical barrier. The role of the antibiotic in such a preparation is to aid the vehicle in its protective function. If extraneous matter contacting the protectant antibiotic preparation contains bacteria, the product will protect from further contamination of the wound and help prevent microbial proliferation. Such a preparation should not encourage the growth of organisms.

The Panel believes that claims for prevention of infection or treatment of infection have not been adequately demonstrated. Note that in the use described as skin wound protectant, the Panel attempted to differentiate between protection against bacterial contamination and infection. The Panel agrees that infection cannot occur without bacterial contamination, but the latter may occur without the former.

An antibiotic added to a product labeled as a skin wound protectant may contribute to the effectiveness by preventing the contamination of a wound with organisms introduced from the environment or by preventing the growth of organisms in the formulations. The Panel recognizes that the same antibiotic in a formulation labeled for prophylaxis or treatment of skin wounds would also have these attributes, but in addition, clinical effectiveness for these indications must be demonstrated prior to labeling of these products for Category I.

B. CATEGORIZATION OF DATA

1. *Category I conditions under which topical antibiotic ingredients are generally recognized as safe and effective as skin wound protectants and are not misbranded.*

Category I active ingredients. The active ingredients generally recognized as safe and effective for use as skin wound protectants and not misbranded are:

Bacitracin
Polymyxin B sulfate
Tetracyclines:
  Chlortetracycline hydrochloride
  Oxytetracycline hydrochloride
  Tetracycline hydrochloride

a. *Bacitracin.* The Panel concludes from its review of the toxicity data in the literature and the submissions to the Panel that bacitracin is safe and effective for topical use in small superficial wounds as a skin wound protectant. Potency (activity) of bacitracin consists of three parts: the unit of potency, which is contained in 13.51 mcg of the bacitracin master standard as specified in 21 CFR 430.6(a)(2); the potency of the bulk antibiotic, which is not less than 40 units of bacitracin per mg as specified in 21 CFR 448.10a(a)(1)(i) (a proposal has been published in the FEDERAL REGISTER of July 16, 1976 (41 FR 29413) raising the potency for topical use to 50 units per mgm); and at least one example of the potency in a finished ointment dosage form, which in this case is 500 units of bacitracin per gm of finished dosage form when formulated into a topical dosage form, as specified in 21 CFR 448.510a(a)(1). The reader is referred to the discussion of bacitracin as a skin wound antibiotic under Category III. (See part IV. paragraph B.3.a. below—Bacitracin.)

(1) *Dosage.* Topical ointment dosage, for both adults and children, should be not less than 500 units of bacitracin per gm of finished ointment dosage form. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(2) *Labeling.* The Panel recommends the Category I labeling for skin wound protectant ingredients. (See part III.

paragraph B.1. below—Category I Labeling.)

b. *Polymyxin B sulfate.* The Panel concludes from its review of the toxicity data in the literature and the submissions to the Panel that polymyxin B sulfate is safe and effective when used in combination with other Category I OTC topical antibiotics for topical use in small superficial wounds as a skin wound protectant. Potency (activity) of polymyxin B consists of three parts: the unit of potency, which is contained in 0.1274 mcg of the polymyxin B master standard as specified in 21 CFR 430.6(a) (4); the potency of the bulk antibiotic, which is not less than 6,000 units of polymyxin B per mg of polymyxin B sulfate on an anhydrous basis, as specified in 21 CFR 448.30a (a) (1); and at least one example of the potency in a finished ointment dosage form in combination with other antibiotics, as specified in 21 CFR 444.542e, which contains polymyxin B sulfate at a variety of potency levels, but generally in the 4,000 to 5,000 unit per gm range (there are no dosage forms certified for polymyxin B sulfate as a single ingredient other than as a urethral irrigant).

It must be recognized that polymyxin B sulfate has a very limited antimicrobial spectrum, which does not include the gram-positive staphylococci or streptococci which commonly infect superficial skin wounds. It should be fully understood that the Panel concludes that polymyxin B sulfate should not be used alone as a single ingredient in a topical preparation for skin wounds, since it may allow selective growth of gram-positive bacteria. This is discussed in the combination section elsewhere in this document. (See part V. paragraph B. below—Classification of Combination Products.) When combined with other antibiotics, polymyxin B sulfate may significantly broaden the spectrum of antimicrobial activity of the product and increase the barrier effect against microorganisms. Despite reports of renal toxicity resulting from injections of polymyxin B sulfate (Ref. 1), the Panel can find no evidence to suggest toxicity from absorption of polymyxin B sulfate through the skin. The reader is referred to the discussion of polymyxin B sulfate as a skin wound antibiotic under Category III. (See part IV. paragraph B.3.d. below—Polymyxin B.)

(1) *Dosage.* Topical ointment dosage, for both adults and children, should be 4,000 to 5,000 units of polymyxin B per gm of finished ointment dosage form when used in combination. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(2) *Labeling.* The Panel recommends the Category I labeling for skin wound protectant ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

REFERENCE

(1) Weinstein, L., "Antimicrobial Agents: Miscellaneous Antibacterial Agents; Antifungal and Antiviral Agents," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., Edited by Goodman, L. S. and A. Gilman, The Macmillan Co., New York, p. 1232, 1975.

c. *Tetracycline preparations (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride).* The Panel concludes fom its review of the literature and submissions to the Panel that tetracycline preparations are safe and effective for topical use as a skin wound protectant for small, superficial wounds.

Potency (activity) of chlortetracycline hydrochloride consists of three parts: the unit of potency, which is contained in 1.0 mcg of the chlortetracycline master standard as specified in 21 CFR 430.6 (b) (3); the potency of the bulk antibiotic, which is not less than 900 mcg chlortetracycline per mg of chlortetracycline hydrochloride as specified in 21 CFR 446.10a(a) (1); and at least one example of the potency in a finished ointment dosage form, which in this case is not less than 1 mg of chlortetracycline hydrochloride per gm of finished ointment, as specified in 21 CFR 446.510a (a) (1).

Potency (activity) of oxytetracycline hydrochloride consists of three parts: the unit of potency, which is contained in 1.13 mcg of the oxytetracycline master standard as specified in 21 CFR 430.6(b) (24); the potency of the bulk antibiotic, which is not less than 835 mcg of oxytetracycline per mg of oxytetracycline hydrochloride on an anhydrous basis as specified in 21 CFR 446.67a (a) (1); and at least one example of the potency in a finished ointment dosage form, which in this case is not less than 30 mg of oxytetracycline per gm of finished ointment, as specified in 21 CFR 446.567b(a) (1).

Potency (activity) of tetracycline hydrochloride consists of three parts: the unit of potency, which is contained in 1.0 mcg of the tetracycline master standard as specified in 21 CFR 430.6(b) (5); the potency of bulk antibiotic which is not less than 975 mcg of tetracycline per mg of tetracycline hydrochloride as specified in 21 CFR 446.80(a) (1); and at least one example of the potency in a finished ointment dosage form, which in this case is not less than 15 mg of tetracycline hydrochloride per gm of an ointment as specified in 21 CFR 446.581a(a) (1).

The reader is referred to the discussion of tetracycline preparations as antibiotics for skin wound treatment under Category III. (See part IV. paragraph B.3.e. below—Tetracyclines (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride).)

(1) *Dosage.* Topical ointment dosage, for both adults and children, should be not less than 1 mg of chlortetracycline hydrochloride per gm of finished ointment dosage form, not less than 30 mg of oxytetracycline per gm of finished ointment dosage form and not less than 15 mg of tetracyline hydrochloride per gm of finished ointment dosage form. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(2) *Labeling.* The Panel recommends the Category I labeling for skin wound protectant ingredients. (See part III. paragraph B.1. below—Category I Labeling.)

Category I labeling. The Panel recommends the following Category I labeling for topical skin wound protectant active ingredients to be generally recognized as safe and effective and not misbranded. Any phrase that is in the definition for that product category or any of the following additional terms may be used:

a. *Indications.* (1) "First-aid product."

(2) "First-aid for small (minor) cuts, abrasions, and burns."

(3) "Protects wounds."

(4) "Protectant."

(5) "Protectant for small (minor) cuts, abrasions, and burns."

(6) "Protects against wound contamination."

b. *Directions for use.* The labeling shall state: "After gentle washing, apply a small amount (an amount equal to the surface area of the tip of a finger) directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily."

c. *Warnings.* (1) *"Caution:* In case of deep or puncture wounds or serious burns see a physician."

(2) "Do not use longer than 1 week."

(3) "If itching, redness, swelling, or pain develops or increases, it may be a sign of infection or allergy. Stop use and see a physician."

(4) "Do not use in the eyes."

(5) "Do not use on long-standing skin conditions such as leg ulcers, diaper rash, or hand eczema."

2. *Category II conditions under which topical antibiotic products are not generally recognized as safe and effective skin wound protectants or are misbranded.*

Category II active ingredients. None listed.

Category II labeling. The Panel concludes that the use of some labeling claims are unsupported by scientific data, nor in some instances by sound theoretical reasoning, and are discussed elsewhere in this document. (See part II. paragraph J.5. above—Category II Labeling.) The Panel classifies the following as Category II labeling claims for skin wound protectant ingredients:

a. "Helps kill bacteria."

b. "Is not an uncommon sensitizer."

c. "Antiseptic."

d. "Aids, speeds, helps, augments, or hastens healing" (or any term or phrase which suggests that there can be decreased healing time resulting from application of an antibiotic-containing product on various cuts, wounds, or abrasions).

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.*

Category III active ingredients. The Panel concludes that available data are

insufficient to permit final classification of the following claimed topical skin wound protection ingredients:

Gramicidin D
Neomycin sulfate

a. *Gramicidin.* The Panel concludes that it has insufficient data to determine whether gramicidin is safe for use in small superficial wounds as a skin wound protectant.

Potency (activity) of gramicidin consists of three parts: the unit of potency, which is contained in 1.0 mcg of the gramicidin master standard as specified in 21 CFR 430.6(b)(17); the potency of the bulk antibiotic, which is not less than 900 mcg of gramicidin per mg as specified in 21 CFR 448.25(a)(1); and at least one example of the potency in a finished ointment dosage form, which in this case is certified only for combinations at 0.25 mg of gramicidin per gm of ointment, as specified in 21 CFR 444.542f (a)(1). Reference is made to the discussion of gramicidin as a skin wound antibiotic under Category III. (See part IV. paragraph B.3.b. below—Gramicidin.)

(1) *Dosage.* Topical ointment dosage for both adults and children should be 0.25 mg of gramicidin per gm of finished ointment dosage form when used in combination. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(2) *Labeling.* The Panel recommends the Category I labeling for skin wound protectant ingredients. (See part III. paragraph B.1. above—Category I Labeling).

b. *Neomycin sulfate.* After careful review of all data submitted, as well as additional evidence provided by the Food and Drug Administration, consultants to the Panel, and an extensive literature search, the Panel concludes that it has insufficient data to determine whether neomycin sulfate is safe for use in small, superficial wounds as a skin wound protectant. These questions include a concern for sensitization and cross-sensitivity and the development of resistance and cross-resistance. This will be discussed in the section on neomycin sulfate as a topical skin wound antibiotic elsewhere in this document. (See part IV. paragraph B.3. below—Neomycin.)

Potency (activity) of neomycin consists of three parts: the unit of potency, which is contained in 1.429 mcg of the neomycin master standard as specified in 21 CFR 430.6(b)(20); the potency of the bulk antibiotic, which is not less than 600 mcg of neomycin per mg of neomycin sulfate as specified in 21 CFR 444.42a(a)(1); and at least one example of the potency of a finished ointment dosage form, which in this case is not less than 5 mg neomycin sulfate (equivalent to 3.5 mg neomycin base) per gm of neomycin sulfate ointment as specified in 21 CFR 444.542a(a)(1). Data for neomycin sulfate are lacking in two areas: (1) the allergic sensitizing potential and the possibility of cross-sensitivity of neomycin sulfate during short-term use on small cuts, burns, abrasions and (2) development of resistance and cross-resistance. (See part IV. paragraph B.3.c.—Neomycin sulfate.)

(1) *Dosage.* Topical ointment dosage for both adults and children should be not less than 5 mg neomycin sulfate (equivalent to 3.5 mgm neomycin base) per gm of finished ointment dosage form. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily, with no maximum daily dosage.

(2) *Labeling.* The Panel recommends the Category I labeling for skin wound protectant ingredients. (See part III. paragraph B.1. above—Category I Labeling.)

Category III labeling. None listed.

IV. Skin Wound Antibiotics

A. General Discussion

The Panel recognizes that topical antibiotics are often used for treatment rather than prevention of infection by the lay public.

The Panel has defined the product category, Skin Wound Antibiotic to be "a safe non-irritating antibiotic-containing preparation which prevents or treats overt skin infection." The role of the antibiotic in such a preparation is to prevent or treat an infection in a small cut, wound, or abrasion. Claims stating or implying these effects against microorganisms must be supported by controlled human studies that demonstrate effectiveness in such treatment.

Sufficient data to prove effectiveness of topical antibiotics for treatment of infected wounds or prevention of such infections are lacking and the Panel has placed these ingredients in Category III. The type of studies to prove effectiveness are discussed below. (See part VI. below—General Guidelines for Safety and Effectiveness Evaluation of Topical Antibiotics.)

B. Categorization of Data

1. *Category I conditions under which antibiotic ingredients for skin wound antibiotics are generally recognized as safe and effective and are not misbranded.*

Category I active ingredients. None listed.

Category I labeling. The Panel recommends the following Category I labeling for topical skin wound antibiotic active ingredients to be generally recognized as safe and effective and not misbranded. Any phrase that is in the definition for that product category or any of the following additional terms may be used:

a. *Indications.* (1) "Decreases bacteria".

(2) "Helps prevent or guard against skin infection".

(3) "Helps reduce the risk (and/or chance) of infection".

(4) "Helps reduce the number of bacteria on the treated area".

(5) "Helps protect wounds against infection".

(6) "First-aid product".

(7) "Broad spectrum (if applicable)".

(8) "Treats infection".

(9) "Antibiotic medication for skin wounds".

(10) Any phrase in the definition of a skin wound protectant.

The Panel believes that the terms listed above are necessary so that OTC drugs will have labeling that is truthful and can be easily understood by consumers.

b. *Directions for use.* The labeling shall state: "After gentle washing, apply a small amount (an amount equal to the surface area of the tip of a finger), directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily".

c. *Warnings.* (1) *"Caution:* In case of deep or puncture wounds or serious burns see a physician".

(2) "Do not use longer than 1 week".

(3) "If itching, redness, swelling or pain develops or increases, it may be a sign of infection or allergy. Stop use and see a physician".

(4) "Do not use in the eyes".

(5) "Do not use on long-standing skin conditions such as leg ulcers, diaper rash, or hand eczema".

2. *Category II conditions under which antibiotic ingredients for skin wound antibiotics are not generally recognized as safe and effective and are misbranded.*

Category II active ingredients. None listed.

Category II labeling. The Panel concludes that the use of certain labeling claims are unsupported by scientific data, nor in some instances by sound theoretical reasoning, and are discussed elsewhere in this document. (See part II. paragraph J.5. above—Category II Labeling.)

The Panel classifies the following as Category II labeling claims for skin wound antibiotic ingredients:

a. "Helps kill bacteria."

b. "Is not an uncommon sensitizer."

c. "Antiseptic."

d. "Aids, speeds, helps, augments, or hastens healing" (or any term or phrase which suggests that there can be decreased healing time resulting from application of any skin wound antibiotic product on various cuts, wounds, or abrasions).

3. *Category III conditions for which the available data are insufficient to permit final classification for skin wound antibiotics at this time.*

Category II active ingredients. The Panel concludes that available data are insufficient to permit final classification of the following claimed topical skin wound antibiotic ingredients:

Bacitracin;
Gramicidin D;
Neomycin sulfate;
Polymyxin B sulfate; and
Tetracyclines (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride).

a. *Bacitracin.* The Panel concludes that while bacitracin is safe in the potency used as a skin wound antibiotic

for application on small areas of the body, there are insufficient data to permit final classification of its effectiveness for use as an OTC skin wound antibiotic. Details of the deficiencies are explained below.

The antibiotic, bacitracin, was first isolated in 1943 by Johnson, Anker, and Meleney. It is produced by a strain of *Bacillus subtilis*.

Chemically, bacitracin is a mixture of polypeptides and has a molecular weight of approximately 1,460. As produced, bacitracin approaches 80 percent purity, with a potency between 40 and 50 units/mgm. Bacitracin, prepared as a zinc salt in petrolatum base, is stable (Ref. 1). The zinc apparently potentiates the action of this antibiotic (Ref. 2). It is unstable in water-containing preparations, and this should be considered when formulating products (Ref. 1).

The mode of action of bacitracin is to interfere with cell wall synthesis of the infecting organism. Mucopeptide linkage is prevented, there is accumulation of nucleotides, and no cell wall formation occurs. The activity is bactericidal. Susceptible organisms are gram-positive cocci, bacilli and corynebacteria. The beta-hemolytic Group A *Streptococcus* is extremely susceptible. Bacitracin is active against penicillin-resistant staphylococci. Gram-negative rods are not affected.

Although bacitracin demonstrates a mode of action like vancomycin and ristocetin, there is no cross reaction with these compounds. Synergism has been observed with penicillin, streptomycin, and neomycin, and occasionally, with tetracyclines and chloramphenicol (Ref. 3).

The development of resistance is poorly identified since laboratory determination of resistance is not normally performed for localized topical infections. There is no known cross resistance to other antibiotics.

The development of resistance to bacitracin is rare and poses no problem for OTC use.

(1) *Safety.* There was only a limited amount of basic toxicological data on bacitracin presented to the Panel. The drug, when administered parenterally to humans, in fairly high doses (200,000 units) for several days, does have nephrotoxic effects (Ref. 3). The evidence in experimental animals to date indicates nephrotoxicity from high doses, but the degree, type, and reversibility of the effect varies greatly with animal species and perhaps with the lot or batch of drug (Ref. 3). Oral administration of bacitracin in doses up to 240,000 units daily in adult humans was not accompanied by side effects or local irritation of gastrointestinal mucosa, and showed virtually no absorption (Ref. 3). Local application to the eyes in solution or ointment form caused no irritation (Ref. 3). It was reported that 5,000 units of bacitracin per ml caused retardation of epithelial regeneration in the eye, but no confirming data were presented (Ref. 4).

It is the Panel's opinion that no potential for harm exists when bacitracin is used on small wounds such as small cuts, abrasions, or burns. When bacitracin is used on large wounds or on large occluded areas there are no data to show the extent of absorption. The Panel recommends no further toxicological work if use is restricted to small areas of application.

BACITRACIN ALLERGY

Literature available to this Panel regarding bacitracin allergy comes predominantly from Europe and relates chiefly to the question of cosensitization with neomycin.

Scandinavian authors, Pirila and coworkers (Refs. 5 through 8) and Hjorth (Ref. 9) have reported frequent cross-sensitivity between neomycin and bacitracin. The concept of cross-sensitivity was defined in the section under neomycin. (See part IV. paragraph B.3.c.—Neomycin sulfate).

Derzavis, Rice, and Leland (Ref. 10) observed one case of dermatitis from bacitracin among 138 patients treated with bacitracin ointment.

In 1959, Pirila and Rouhunkoski (Ref. 6) reported 96 patients allergic to a 10 percent solution of bacitracin.

While combined sensitivity (occurring to both drugs at the same time) has been reported as a frequent experience in Europe, it was noted in 1963 by Epstein and Wenzel (Ref. 11), that only seven out of 173 North American dermatologists reported that they had observed sensitivity to bacitracin in neomycin-allergic patients. Epstein and Wenzel note that combined sensitivity to neomycin and bacitracin was often observed in Finland, Denmark, and Norway, but not in Sweden and other countries (Ref. 11). These authors, quoting Danbolt and Hellerstrom (Ref. 11), suggest that the differences are due to the fact that these antibiotics were sold over-the-counter in Norway, Denmark, and Finland, but not in Sweden. The antibiotic ointments most commonly used in Finland and Denmark contained both neomycin and bacitracin. Epstein and Wenzel believed that independent sensitization to both neomycin and bacitracin was a more plausible explanation for this discrepency than cross-sensitivity.

Coumaish (Ref. 12) presented a patient who developed an anaphylactoid systemic reaction (very serious allergic or sensitization type reaction) on three occasions following the topical application of neomycin and bacitracin (without enzymes) to a varicose ulcer.

Roupe and Strannegard (Ref. 13) reported a case of anaphylactic shock following topical application of an ointment containing bacitracin and neomycin in a 14-year-old girl. Anti-bacitracin antibodies were demonstrated in the patient's serum. Both cases involved large areas of skin that were particularly raw or ulcerated, which facilitated the absorption of large quantities of neomycin and bacitracin. These are the only cases reported in the literature and are not of concern in OTC use of bacitracin.

The North American Contact Dermatitis Research Group (Ref. 14) did not feel that bacitracin was a sufficiently frequent cause of skin allergy to include it in their 1972 study on the most common causes of allergy skin disease in North America.

(2) *Effectiveness.* Bacitracin for topical use was evaluated originally in clinical trials performed between 1947 and 1954 (Refs. 15 through 21).

These studies lacked controls and involved a wide variety of superficial skin infections. The dosage forms tested included bacitracin ointment and bacitracin aqueous solution. The later is not available commercially (either OTC or through prescription) for topical use.

In 1947, Meleney and Johnson (Ref. 15) reported on the use of bacitracin ointment and bacitracin aqueous solution in 100 patients with assorted minor surgical infections. Results were good in 31 percent, moderate in 57 percent, and poor in 12 percent. No controls were included, and results using bacitracin ointment alone could not be extracted from the report.

In 1948 and 1949 Miller et al. (Refs. 16 and 17) reported uncontrolled studies using bacitracin ointment in 87 and 68 adequately followed patients with several types of superficial skin infections. Impetigo cases responded particularly well to treatment, with a median healing time of 8 days among 42 of 44 patients cured with bacitracin ointment. However, no cases were treated with the ointment base alone.

In 1949 Eichenlaub and Olivo (Ref. 18) treated 50 cases of assorted skin infections with bacitracin ointment, with results being good in 33, moderate in 11, and poor in 6 patients. Among 11 impetigo cases, 10 were cured. No cultures were performed and no controls were included in this study. Finnerty (Ref. 19) in 1951 treated 75 cases of superficial skin infection with bacitracin ointment or bacitracin solution in wet dressings. Results were good in 46, moderate in 27, and poor in 2 patients. All 12 impetigo cases were cleared in an average of 7 days. No cultures or controls were included in the study, and results using bacitracin ointment alone could not be extracted. In 1951 Wrong et al. (Ref. 20) reported on a very small uncontrolled clinical study using bacitracin ointment. Among 27 patients with assorted skin infections, results were good in 6, moderate in 16, and poor in 5 patients. Cultures were included in this study, but no control ointment was used. In 1949 Derzavis and Rice (Ref. 21) treated 138 patients with various superficial and deep bacterial infections. Results were good in 128, moderate in 5, and poor in 5 patients. All 46 patients with impetigo were cured with bacitracin ointment in an average time of 4.7 days. No cultures or controls were included in the study.

In 1962 Klainer et al. (Ref. 22) reported that bacitracin ointment was used to stop an epidemic of *Staphylococcus aureus* infection in a hospital newborn

nursery. Bacitracin ointment was applied twice daily to the umbilical area, inguinal folds, and suprapubic area of 166 infants. Prior to the treatment period, 79 percent of 52 infants had the epidemic strain of *Staphylococcus aureus*. During the treatment period, only 2 percent of 39 newborn infants treated with bacitracin ointment had positive cultures of staphylococci from the navel, groin, or nose. In contrast, 52 percent of 23 untreated control infants during the same period were positive for staphylococci. The overall incidence of staphylococcal infections in the nursery during the treatment period was 22 percent. Immediately after the treatment period, cultures of 133 infants revealed 21 percent to be positive for *Staphylococcus aureus*, but the epidemic strain had been eliminated. Bacitracin ointment was felt to have been very effective in eliminating the reservoir of epidemic staphylococci and preventing cross-infection between infants.

In 1970 Dillon (Ref. 23) performed the only double-blinded, carefully controlled studies involving bacitracin ointment of which the Panel is aware. He compared the effects of bacitracin ointment, hexachlorophene scrubs, benzethine penicillin G, and procaine penicillin in the treatment of 531 children with impetigo. Bacterial cultures were done on each patient. In the first study which involved 110 children, after 2 weeks of treatment, clearing of impetigo occurred in 9 percent of 22 children treated with hexachlorophene alone, 39 percent of 46 children treated with hexachlorophene and bacitracin ointment, 83 percent of 18 children treated with hexachlorophene and oral penicillin V, and 96 percent of 24 children treated with hexachlorophene and intramuscular penicillin G. It was concluded that topical treatment of impetigo with bacitracin ointment combined with hexachlorophene was better than treatment with hexachlorophene alone, but was markedly inferior to treatment with intramuscular penicillin. This conclusion was based on slower rates of healing, continued development of new lesions, and the continued presence of pathogenic streptococci in the respiratory tract. Practical difficulties in application of bacitracin ointment three times daily were encountered when numerous lesions needed treating or more than only family member needed treatment. Since 1970, the systemic treatment of impetigo has generally been recognized to be superior to any type of topical therapy. Although some benefit was obtained from adding bacitracin topical therapy to hexachlorophene scrubs in the above study, the Panel concludes that the cure rate of 39 percent is not satisfactory in treatment of such a highly transmissible and infectious disease as impetigo.

Dillon reported a recent unpublished uncontrolled study (Ref. 24) to the Panel in which ointment containing bacitracin was used to treat 64 children with fewer than five impetigo lesions each. Gentle washing of lesions with a coarse soapy cloth was followed by application of bacitracin ointment 4 times daily. Cultures of lesions revealed 20 cases with pure staphylococci, 40 cases with mixed staphylococci and streptococci, and 4 cases with no growth. Results after 10 to 14 days of treatment showed clearing in 60 percent of the pure staphylococcal lesions, 90 percent of the mixed staphylococcal-streptococcal lesions, and 100 percent of "sterile" lesions, with overall clearing in 81 percent of cases. Nose and throat cultures taken before and after treatment showed almost no change in the pathogenic staphylococci and streptococci in the respiratory tract. This source was felt to possibly account for the reinfection of skin observed in five patients with new lesions following treatment. Patients not improving after 5 to 7 days of bacitracin ointment treatment were treated with oral antibiotics. Although this study was uncontrolled, Dillon felt that clinical improvement was significant and that bacitracin ointment should be considered superior to soap and water scrubbing for treatment of the early mild cases of impetigo. The Panel interpreted his remarks as favoring continued OTC availability of bacitracin ointment.

(3) *Dosage.* Topical ointment dosage, for both adults and children should be not less than 500 units of bacitracin per gm of finished ointment dosage form. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for skin wound antibiotic ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* In summary, the Panel concludes that bacitracin requires controlled clinical evaluation to establish prophylactic and therapeutic effectiveness. Bacitracin appears to be a safe antibiotic for OTC use, with no evidence of either toxicity or sensitization hazards resulting from use on small areas of infected skin.

Some evidence presented above suggests that bacitracin may be helpful in preventing and treating superficial skin infections caused by staphylococci and streptococci. However, no controlled studies were presented to the Panel showing that bacitracin ointment was therapeutically superior to its ointment base alone for treating such infections. The only well-controlled, double-blinded study (Ref. 23) seemed to question the advisability of using bacitracin ointment for treating superficial bacterial infections such as impetigo, since systemic antibiotics produce a much more rapid and reliable cure of the infection.

The Panel recognizes that systemic antibiotics may not always be readily available for treatment of impetigo or other superficial skin infections, and that an effective OTC product would be desirable. The uncontrolled study by Dillon (Ref. 24) indicates that bacitracin ointment is frequently effective in treating mild impetigo in its early stages. If controlled studies confirm this impression and show that other types of early infections in superficial skin wounds may be aborted by application of bacitracin ointment, bacitracin should be moved into Category I.

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b. *Gramicidin D.* The Panel concludes that there are insufficient safety and effectiveness data to permit final classification of gramicidin D as a skin wound antibiotic.

An antibiotic mixture was obtained from a culture of a soil organism, *Bacillus brevis*, in early antibiotic work by Dubos in 1939. The mixture was called *tyrothricin* and its two components were *gramicidin* (20 percent) and *tyrocidine* (80 percent) (Ref. 1). They are polypeptide in nature and extracted from acidified cultures with alcohol and sodium chloride. The crude material is a gray to brown powder which is stable to light, air, and temperatures up to 50° C. It is practically insoluble in water (Ref. 1), but solution can be accomplished by the addition of suitable surface active agents. It is soluble in alcohol and glycols and has a high heat stability (Ref. 1). By extraction with equal amounts of acetone and ether the gramicidin may be separated from the tyrocidine. It may be concentrated by vacuum and redissolved in hot acetone. Several gramicidins are described in the "Merck Index" including gramicidin D, the only gramicidin under consideration by the Panel (Ref. 2). Gramicidin D is that described and developed by Dubos and has a molecular weight of approximately 2,000 gm/mole. Gramicidin J_1 and J_2 have been described by the Japanese but are apparently not used clinically. Gramicidin S is also known as gramicidin C and is described in the Russian clinical literature. Gramicidin S differs from gramicidin D in that the molecular weight of gramicidin S is reported to be 1,140 gm/mole.

As the analyses became more sophisticated, it was realized that the tyrocidine fraction was inactive, so that the active drug entity of tyrothricin is gramicidin. The inactive tyrocidine is not marketed.

Gramicidin is bactericidal (Ref. 1). Its activity is directed against the cell membranes of susceptible organisms. Both aerobes and anarobes are susceptible. Mycobacteria and streptococci are senitive. The antibiotic is largely inactive against gram-negative organisms (Ref. 1).

Phospholipids inhibit the activity of gramicidin and this is probably the explanation for the resistance of gram-negative bacilli, which have phospholipids on their surfaces.

There are no reports of resistance developing to this antibiotic.

(1) *Safety.* The Panel is aware that a limited amount of gramicidin D could possibly be absorbed from the application of a preparation to a small cut or abrasion. There were no toxicity data submitted on gramicidin. The Panel is concerned about any amount that is absorbed. Therefore, the Panel recommends that sufficient toxicological work be performed to show that the amount that could be absorbed from a small wound is safe. This information should include target organ toxicity studies with a determination of the blood level required to elicit the toxic response as described in testing guidelines. From these data, the safety of an applied dose could be assessed.

Gramicidin is a potent hemolytic agent causing destruction of red blood cells (Ref. 1). Hemolysis may occur if gramicidin is employed in fresh surgical or traumatic wounds.

On the basis of the limited data submitted that are available in Goodman and Gilman (Ref. 1), the Panel cannot make an adequate judgment about the safety of gramicidin at this time. Though there is no evidence of a serious toxicological hazard from the limited topical use, there is also no evidence of its safety.

The Panel would therefore require basic toxicological data including MLD, LD–50 and LD–99. Because gramicidin is a hemolytic agent, the Panel would require studies in this area sufficient to assess this risk.

The Panel has reviewed the literature in regard to the allergenicity of topical gramicidin D. The literature does not indicate that gramicidin D is a cause of allergic skin disease.

(2) *Effectiveness.* Gramicidin D, 0.25 mg/gm in plasticized hydrocarbon gel base, has been submitted for OTC review as part of a combination ointment containing neomycin. The Panel has been unable to find any literature regarding either the safety or efficacy of this product or of any ointment containing only gramicidin D. Gramicidin S, a slightly different form of gramicidin, was used in an ointment base in 1944 by Sergiev (Ref. 3) in a collaborative study among 10 hospitals in Russia. However, gramicidin S solution was used at the same time and results of treatment attributable to gramicidin S ointment cannot be extracted from the report.

With so little data available on gramicidin, and since gramicidin is the active antibiotic component of tyrothricin, the literature on tyrothricin was reviewed by the Panel in an effort to evaluate possible clinical effectiveness of gramicidin D. Most reports date from the 1940's and are uncontrolled clinical studies involving approximately 1,300 patients with infected skin diseases or superficial surgical wounds. Tyrothricin was used mainly in the form of topical wet dressings in aqueous solution containing 0.5 mg/ml, a dosage form which is not available commercially. Only two studies (Refs. 4 and 5) discussed below included clinical trials using tyrothricin in ointment or vanishing cream base.

In 1946 Anderson found tyrothricin to be bacteriologically inactive in seven different ointment bases when tested with in vitro techniques (Ref. 6). The Panel has seen no other data concerning in vitro activity of tyrothricin or gramicidin in either ointment or cream bases.

Reported clinical trials with tyrothricin ointment or cream lack consistency and have been extremely limited, involving only about 70 patients with a wide variety of skin diseases. In 1948 Johnson tested tyrothricin cream containing 1.0 mg/gm in 10 patients with impetigo (Ref. 5). Although well tolerated and resulting in clearing of lesions after 6 to 12 days, the tyrothricin cream did not provide as rapid healing of impetigo as either penicillin ointment or ammoniated mercury ointment used variously as controls. No comparison was made to treatment using cream base alone. In the same study, tyrothricin cream was of little benefit in treating 14 other patients with superficial infections, and was concluded to be of "little practical value." In 1946 Franks et al. treated 47 cases of skin infection with either tyrothricin ointment 0.3 mg/gm in greaseless base or tyrothricin solution (Ref. 4). While impetigo lesions cleared after approximately 6 days in the eight cases treated, no other skin infections were cured. No distinction was made between patients using tyrothricin ointment or solution, making therapeutic results obtained with ointment impossible to extract or interpret.

In 1946 tyrothricin solution in either water or alcohol base was shown to be active against staphylococci and streptococci in vitro (Ref. 6). The same study reported a small uncontrolled clinical trial with alcoholic tyrothricin solution 40 to 200 mg/ml used as continuous wet dressings in 20 patients with assorted skin infections. "Good" results occurred in 15 patients, but were not fully explained.

The use of tyrothricin solution was reported in several other small uncontrolled studies (Refs. 7 through 12) which did not deal with conditions normally treated with OTC topical antibiotics. In 1942 Rammelkamp (Ref. 7) treated leg ulcers using tyrothricin in alcohol. Ulcers containing *Staphylococcus aureus*, hemolytic streptococci, or *Streptococcus fecalis* healed completely in 6 of 12 patients. Ulcers did not respond if they contained gram-negative organisms. Rankin in 1944 (Ref. 8) felt that marked tissue stimulation occurred in six chronic leg ulcers treated with tyrothricin aqueous solution, with complete healing of five ulcers. Kvale et al. in 1944 (Ref. 9) treated 50 leg ulcers with tyrothricin solution and also thought that marked stimulation of granulation tissue occurred. However, there were no controls or statistics to support this conclusion. Merrell, in an uncontrolled study in 1943 (Ref. 10), felt that tyrothricin solution helped prepare ulcers for skin grafting, reporting favorable results in 53 percent of 93 cases of infected ulcers and wounds. In 1946 Mom and Bernal (Ref. 11) treated infected leprosy ulcers on the legs with tyrothricin solution, with healing of most ulcers within 75 days. The Panel concluded that this study was not relevant to OTC use of topical antibiotics

due to the nature of the underlying disease. In 1948 Lask (Ref. 12) used tyrothricin solution to treat a small number of stasis ulcers present longer than 1 year, with complete healing of ulcers in 9 of 14 patients within 12 weeks. In the same uncontrolled study, 10 granulating wounds were treated daily with tyrothricin solution in preparation for skin grafting, with rapid elimination of streptococci from all wounds.

Postoperative wounds have been treated with tyrothricin solution (Refs. 13 through 15). Cantor in 1946 (Ref. 13) concluded that postoperative proctologic wounds, such as hemorrhoidectomy wounds, treated with tyrothricin aqueous solution in wet dressings developed less drainage and infection and permitted earlier ambulation than usual. No controls were included and no mention was made of the number of patients treated. In 1947 Goldman et al. (Ref. 14) treated 62 postoperative pilonidal cysts with tyrothricin solution and observed that granulation tissue appeared to be cleaner, and healing appeared to be more rapid than usual. No consistent controls were included in this study.

In 1946 Kozoll et al. (Ref. 15) treated 77 surgical infections with tyrothricin solution 0.5 mg/c, including postoperative wounds, leg ulcers, abscesses, and burns. Excellent results ocurred within 2 months in 65 percent of cases, with disappearance of visible signs of infection. Doubling the concentration of tyrothricin appeared to increase the rate of granulation tissue formation. The only controls included were in a small, paired-comparison study involving six patients with bilateral leg ulcers. In four of the six patients faster healing occurred in ulcers on the sides treated with tyrothricin than one sides receiving plain solution.

Minor surgical infections, including cellulitis, furuncles, and acute paronychia were treated with tyrothricin solution by Goldman et al. (Ref. 14). In 43 patients, there was rapid disappearance of discharge and development of granulation tissue. Control medications were applied in a few cases bupt not in a consistent manner. McKee et al, in 1946 (Ref. 16) used tyrothricin solution in 232 patients with hair follicle infections. The tyrothricin solution, containing a special propylene glycol vehicle to increase penetration into the skin, produced a favorable response in most patients. Controls included 15 patients with acne or follisulitis treated for 3 weeks with either the vehicle alone or tyrothricin in ethyl alcohol solution. Although the control patients failed to improve in 3 weeks, the Panel concluded that their number was too small and their diseases were too varied to be significant.

(3) *Dosage.* Topical ointment dosage, for both adults and children, should be 0.25 mg of gramicidin per gm of finished ointment dosage form when used in combination. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for skin wound antibiotic ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

(5) *Evaluation.* In summary, the Panel concludes that gramicidin D requires controlled clinical evaluation to establish prophylactic and therapeutic effectiveness. In addition, further safety data are required since there were no toxicological studies concerning gramicidin D reported to the Panel. The Panel recommends that the safety of gramicidin D be studied to determine both systemic and topical toxicity, as outlined in the Safety Testing Protocol described elsewhere in this document. (See part VI. below—General Guidelines for Safety and Effectiveness Evaluation of Topical Antibiotics). Specifically, the amount of gramicidin D absorbed through the skin following topical application of gramicidin D cream or ointment needs to be determined, as does the hemolytic (red blood cell breakdown) potential of gramicidin D resulting from absorption through fresh superficial wounds. The Panel concludes that the toxicity potential of this antibiotic has apparently never been documented.

Clinical studies utilizing purified gramicidin are also apparently nonexistent. Evaluation of the clinical effectiveness of gramicidin therefore depends on several uncontrolled studies performed in the 1940's using tyrothricin, which contained gramicidin as its active component. While some studies indicated that tyrothricin might be helpful in treating wounds infected with staphylococci and streptococci, most studies utilized tyrothricin solution, a dosage form not presently available for OTC use. Little data exist from use of tyrothricin in either cream or ointment bases, the currently accepted OTC dosage forms. The Panel considers that it is not scientifically sound to extrapolate data from studies using tyrothricin solution in attempting to evaluate the clinical effectiveness of gramicidin in ointment form. The Panel recommends that effectiveness data using gramicidin alone be acquired in controlled clinical studies involving treatment of minor cuts, wounds, burns, and abrasions.

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c. *Neomycin sulfate.* After careful review of all data submitted and additional evidence provided by FDA, consultants to the Panel, and an extensive literature search, the Panel concludes that there are insufficient safety and effectiveness data to permit final classification of neomycin sulfate as a skin wound antibiotic. Data for neomycin sulfate is lacking in three areas: (1) the allergic sensitizing potential and the possibility of cross-sensitivity of neomycin sulfate during short-term use on small cuts, burns, and abrasions, (2) the therapeutic and prophylactic effectiveness of neomycin sulfate when used on small cuts, burns, and abrasions, and (3) development of resistance and cross-resistance. Details of these deficiencies in data submitted on the safety and effectiveness of neomycin sulfate will be expanded in the following sections.

The antibiotic, neomycin, is produced by a soil organism, *Streptomyces fradiae.* It was first isolated in 1949 by Waksman and Lechevalier (Ref. 1).

Neomycin is an aminoglycoside antibiotic containing a deoxystreptamine moiety and therefore is related to streptomycin, gentamicin, paramomycin and kanamycin (Ref. 1) and two newer aminoglycoside antibiotics, amikacin and tobramycin. The complex constituting neomycin includes three components, neomycin A, B, and C. While the proportions of these may vary in different preparations, commercial neomycin consists almost entirely of the B component (Ref. 1).

The mode of action of neomycin is to interfere with protein synthesis of the microbial cell and is considered bac-

tericidal. A number of organisms frequently show in vitro susceptibility with 5 to 10 mcg/ml (ppm), or less, of neomycin (Ref. 1). Among these are *Staphylococcus aureus, Streptococcus* species, *Proteus* species, *Escherichia coli* and *Corynebacterium* species.

Clinical strains of *Staphylococcus aureus* that are neomycin resistant are always resistant to kanamycin (100 percent cross-resistance). Cross-resistance to other aminoglycoside antibiotics may be complete or only partial (Ref. 1). In fact, kanamycin is the representative antibiotic of the aminoglycoside family (class) of antibiotics used in susceptibility testing to determine resistance in clinical isolates (bacteria grown out of a clinical lesion). Kanamycin is still used in systemic infections, while neomycin is generally restricted to topical application or to presurgical reduction of gastrointestinal flora.

The mechanism of resistance for both neomycin and kanamycin is considered to come from bacterial enzyme (phospho-transferase) inactivation of the antibiotic (Ref. 1).

Neomycin has also been used in deodorant products to supress axillary odor. Shehadeh and Kligman (Ref. 2) in 1963 applied an aqueous solution to one axilla (underarm) and an inert vehicle to the other axilla of 50 males for 15 to 16 weeks. Neomycin was found to suppress axillary odor while eliminating all gram-positive bacteria and allowing the gram-negative flora to become dominant. It is known that organisms that are susceptible to antibiotics may lose their susceptibility and develop resistance on exposure to low levels of antibiotics over a short (streptomycin-like, one-step resistance) or over a long (penicillin-like, step-wise resistance) period of time, both in vitro and in vivo. Since short-time resistance development was first detected as a one-step change in the organism exposed to streptomycin, it is often referred to as streptomycin-like; one-step resistance. When a longer time is required to show resistance development, such as is required for induction of the enzyme penicillinase to product resistance, it is often referred to as penicillin-like, step-wise resistance. In these studies, no organisms were found to be resistant to neomycin and the axillary flora returned to its normal balance within 4 weeks after neomycin was discontinued (Ref. 2).

The development of resistant strains of bacteria following topical application of neomycin was investigated by Livingood, et al., (Ref. 3) and published in 1959. Cultures from 354 patients before and after treatment with either topical neomycin, tetracycline, erythromycin, or bacitracin ointments revealed no *Staphylococcus aureus* organisms remaining after neomycin treatment of 109 cases. In contrast, the picture was somewhat different where 16 isolates of resistant *Staphylococcus* organisms were found among 136 patients treated with tetracycline or erythromycin ointment. Marples and Kligman in 1969 (Ref. 4), some 10 years later, demonstrated development of neomycin-resistant *Staphylococcus* organisms with neomycin aqueous solution used experimentally under occlusion on opposite forearms of 10 subjects. This organism's presence resulted in a pyoderma and became the dominant organism in 7 out of 10 neomycin-treated arms.

A comprehensive review article on resistance of *Staphylococcus aureus* to antibiotics appeared in March 1975 (Ref. 5). Development of neomycin resistance is summarized in the review. Lacey pointed out that resistance to neomycin had not been seen in the first 8 to 10 years (1951–1959) of its use, but suddenly appeared around 1960 despite early widespread topical use. The strains discovered were already resistant to several antibiotics and were closely related according to phage typeability studies. These strains were isolated frequently from patients treated with topical neomycin. Epidemiologic studies suggested that the topical application of neomycin played a greater role than the systemic use of related antibiotics in the development of resistant strains. Since enormous populations of staphylococci were exposed to neomycin, Lacey postulated that the delay in resistance development over the initial 8- to 10-year period of use was related to the rarity of the resistance genes in the populations of staphylococci exposed (Ref. 5). Since resistance genes are plasmid-borne (contained within the cytoplasm of the cell) and are relatively rare, the appearance of resistance in numerous staphylococcal phage types indicates that gene transfer from the original resistant phage type must have occurred and also indicates the presence of a transducing phage. While the complete interrelationships have not been worked out experimentally or clinically, it would appear that the topical application of neomycin throughout the general population could potentially play a role in the increase of resistant organisms, not just to neomycin but to other related aminoglycoside antibiotics such as kanamycin, gentamicin, amikacin, tobramycin, and other potentially life-saving systemic antibiotics, some of which are now in the developmental stage.

There are some suggestive data that organisms such as *Staphylococcus epidermidis* show increased resistance to kanamycin. Routine susceptibility tests use kanamycin to predict resistance to aminoglycoside antibiotics. Since there is 100 percent cross-resistance between neomycin and kanamycin, it can be assumed that hospital clinical isolates of *Staphylococcus epidermidis* are also neomycin resistant. The information concerning the current resistance of *Staphylococcus aureus* or the streptococci from nonhospital infections in the community at large are not available. This may be due in part to lack of routine or systematic susceptibility testing by dermatologists or pediatricians when superficial infections are treated.

Resistance to neomycin confers resistance to other deoxystreptamine-containing antibiotics.

Resistance has been seen commonly in the *Pseudomonas* species, especially in strains of *Pseudomonas aeruginosa*. Other organisms in which some resistance has been demonstrated are: *Staphylococcus aureus, Enterobacter, Streptococcus, Clostridium* and *Mycobacterium*. The fungi and viruses are quite resistant to neomycin (Refs. 6 through 22).

The Panel is concerned that the neomycin resistance of skin staphylococci in the population may have a deleterious effect if the staphylococci are cross-resistant to other aminoglycoside anitibiotics used for serious systemic infections.

(1) *Safety.* Shortly after its discovery in 1949, neomycin sulfate was administered to man as a "so-called" broad spectrum antibiotic. It was found to be so toxic when administered parenterally that its use is now largely restricted to topical applications. The known toxicology of neomycin will be fully discussed below. The Panel has determined that the amount of neomycin that could be absorbed from application to small wounds is far below the toxic level. Thus, for such uses, the Panel has determined that systemic toxicity from topical application of neomycin sulfate is unlikely. However, the following full discussion of the toxicity potential drawn from the available data does give the reasons why the Panel believes that the label restrictions against use on large areas of diaper rash, heat rash, and burns are fully justifiable.

It is now recognized that the use of neomycin sulfate by injection, in high doses, over a period of time in man produces neurotoxic deafness and kidney damage. There seems to be great individual variation in susceptibility to the toxic effects of neomycin (Ref. 23). Preexisting renal insufficiency may cause accumulation of the drug in body fluids and tissues (Ref. 23). The minimal blood concentration required to produce neurotoxic and nephrotoxic effects is unknown. At least two authors (Refs. 23 and 24) have recommended that parenteral doses of 1 gm daily for 1 week should not be exceeded. There are no firm data to support this dose level as safe, but some data do exist suggesting that lower doses for longer than one week induce only transient kidney damage.

It has been previously stated that the parenteral toxicity of neomycin sulfate has largely limited its use to topical application. However, the amount of neomycin that may be absorbed into the blood stream after topical application of neomycin sulfate to diseased skin is unknown. The absorption of neomycin after topical application to normal skin is reported to be very low. In a study in adult males, extensive exposure of normal skin for 6 hours to neomycin sulfate ointment applied over large areas of body surface did not result in any detectable percutaneous absorption (Ref. 25). However, inflamed and damaged skin

and mucous membranes have been found to lack the normal barriers to neomycin absorption (Ref. 24). One report showed renal failure and deafness following the use of neomycin and porcine xenografts (skin grafts from a hog) in a burned patient. The blood level of neomycin in this deafened patient was 4.5 mcg/ml 3 days after the last exposure (Ref. 26). Whether or not deafness can occur with lower blood levels of neomycin is not known.

A report (Ref. 27) in which neomycin was administered subcutaneously to humans included blood serum assays for neomycin performed at various dosage levels after various periods of time. A single subcutaneous injection of 1.0 gm of neomycin produced serum levels of approximately 20 mcg/ml for at least 8 hours and resulted in mild signs of renal impairment in one of four patients. No evidence of toxicity appeared from a single subcutaneous injection of 500 mg, although serum neomycin levels were 10 mcg/ml for at least 8 hours. Multiple injections of neomycin every 4 to 6 hours for 15 to 16 days produced ototoxicity with some impaired renal function if serum concentrations of neomycin were 15 to 16 mcg/ml for 15 days. Whether or not lower blood concentrations of neomycin over a period of time would lead to renal damage was not determined. Another study (Ref. 28) demonstrated serum levels of neomycin 12 to 30 mcg/ml following intramuscular injections of 300 mg every 6 hours for four doses. In cases of renal impairment, there was a significantly rapid buildup in serum concentration of neomycin. The blood concentration required over a definitive period of time as necessary to cause renal or ototoxic (deleterious to hearing and balance) effects cannot be assessed from any of the available data.

There have been other reports of deafness occurring in human patients following topical application of neomycin. Murphy (Ref. 29) reports deafness resulting from instillation of neomycin into the inner ear. Kelley et al. (Ref. 30) report of deafness following irrigation of granulating wounds with neomycin solution.

In animals, neomycin shows rather specific toxicities when administered parenterally. The acute LD_{50} in mice by intraperitoneal injection was found to be about 200 mg/kg (Ref. 23). Somewhat smaller doses of 40–100 mg/kg/day given to cats for 8–60 days caused neurotoxic effects. Kidney lesions developed in dogs and rats at similar dose levels given for 1–3 weeks (Refs. 23 and 24). Topical neomycin in ointment form or aqueous solution was not acutely irritating to eyes of dogs or rabbits and produced no dem- of dogs or rabbits and produce no demonstrable skin irritation (Ref. 25).

It is obvious from the above discussion that induction of neurotoxic and nephrotoxic symptoms is both time and dose dependent. In general, at lower blood concentrations, toxic manifestations require up to several weeks to become noticeable, while at higher blood concentrations the effect is detectable sooner. The Panel concludes that it would be most unlikely that detectable blood levels could be obtained from application of neomycin sulfate preparations to small wounds such as cuts and abrasions. The Panel recognizes that toxic blood levels can be reached if neomycin sulfate preparations are placed on large areas of burned or broken skin.

In summary, the Panel concludes that absorption of neomycin from small cuts, abrasions, or burns would not be sufficient to induce either neurotoxic effects or nephrotoxic effects, especially since these products are labeled "not to be used for more than 1 week." Therefore, for restricted use on small areas, the Panel does not recommend further toxicological study. If neomycin sulfate preparations are to be used on large burns, abrasions, or under large occluded areas, the Panel believes that the evidence presented suggests that a toxicological hazard may exist. It is the conclusion of the Panel that neomycin sulfate should be restricted from use in OTC medications labeled for use on large areas of the skin.

(i) *Neomycin allergy.* Some of the antibiotics have a history of inducing allergic contact dermatitis upon topical application. The following discussion relates to modes of recognizing and testing for allergic skin disease. The Panel is discussing and evaluating the current and accepted testing procedures in order to place the reported prevalence of allergic skin disease in proper perspective.

The allergic reactions caused by topical antibiotics are usually of the allergic contact dermatitis type. Contact dermatitis is characterized by redness, scaling, itching, and/or blistering of the skin. It is caused by one or more chemicals contacting the skin surface for a variable length of time. Two types of contact dermatitis exist: allergic contact dermatitis which develops slowly and only affects certain people following repeated exposure to sensitizing chemicals such as an antibiotic, poison ivy resin, or formaldehyde; and irritant contact dermatitis, which is not allergic and often develops rapidly in any person following skin contact with irritating chemicals such as soap or lye solution.

In discussing the safety of topical antibiotics with reference to development of allergic reactions, the Panel is concerned mainly with neomycin. All other topical antibiotics discussed in this monograph (bacitracin, gramicidin, polymyxin, and tetracycline) appear to cause little allergic sensitization. The reader is referred to detailed discussions of the allergenicity of each antibiotic later in this report.

The development and extent of allergic contact dermatitis depends on several factors (Ref. 31). These include: the age of the patient; the duration and frequency of exposure; the underlying innate ability of the patient to develop allergic sensitivity; the part of the body exposed to sensitizing chemicals; the presence of infected or inflamed, eczematized (rough, scaly) skin; the amount of perspiration; the degree of pressure and friction bringing chemicals into contact with the skin; the type of base used in the commercial product; the concentration of the active sensitizing ingredient; and the inherent sensitizing potential of the active ingredient.

The physician's diagnosis of allergic contact dermatitis is confirmed using the technique of patch testing. The test patch is a small cotton gauze, or cellulose disc covered with test material, which exposes a small portion of skin to a potentially sensitizing chemical. Several patch tests are usually applied simultaneously to the back and covered with occlusive tape which holds them in place for 48 hours. The patches are then removed and the underlying skin examined for evidence of dermatitis 24 hours later. This 48-hour closed patch has become the international standard of testing (Refs. 32 and 33).

Unfortunately, the results of patch testing must be evaluated in light of the fact that its use and misuse is well documented (Refs. 31 and 34). The proper testing concentration for each chemical must be determined by studying normal control volunteers. Too low a concentration results in false negative tests (Ref. 35), while excessive concentrations lead to false positive tests from chemical irritation of the skin. To be considered valid, a patch test must be proved to be relevant to the case of dermatitis in question. Relevance is said to be present if contact with a commercial product containing a patch-test-positive material for the patient produces allergic contact dermatitis. Not all publications reviewed by the Panel established relevance of positive patch tests. However, the major studies of the International Contact Dermatitis Research Group attempted to eliminate the nonrelevant test responses (Ref. 32).

(ii) *The atopic state and its relationship to allergic contact dermatitis.* Comments have been made that the segment of the population at large, who are atopic, are more vulnerable to allergic disease than the normal individual. Current scientific evidence refutes the validity of this concept as is explained in the following discussion. Development of allergic contact dermatitis to topical medications was long considered to be dependent on the presence of underlying atopic dermatitis (Refs. 36 and 37). Atopic dermatitis is an inherited condition frequently associated with allergic problems such as asthma, hay fever, and hives. The skin of people with atopic dermatitis is very dry, itchy, and easily irritated by contact with mild chemicals such as soaps. However, despite their tendency to frequently develop irritant contact dermatitis, patients with atopic dermatitis have recently been found to be less reactive to topically applied sensitizing chemicals than normal control patients (Ref. 38). Their skin is less apt to react in an allergic manner to chemicals which come in contact with it than is normal skin or skin with other diseases. They have also proved to be more difficult to sensitize than control patients using topical DNCB (2, 4-dinitrochlorobenzene), a very potent topical sensitizer (Ref. 39).

The apparent altered immune state associated with atopic dermatitis is thought to be due to increased levels of immuoglobulins which lower cellular immunity to bacterial and viral infections (Ref. 40). It seems clear from the work of Gottlieb and Hanifin that an immunoglobulin IgE may itself prevent in vitro cellular immune responses (Ref. 41). However, it is still not clear whether patients with atopic dermatitis are deficient in cellular immunity, even though they have selective ability to become sensitized to certain antigens.

In a study of 752 patients with various types of eczematous dermatitis (allergic skin condition), Wereide tried to determine the incidence of allergic contact dermatitis produced by a number of agents (Ref. 42). He found an incidence of 2.3 percent neomycin positive patch test reactions in a group of 43 patients with atopic dermatitis. This was in sharp contrast to an incidence of 20.8 percent neomycin allergic patch test reactions in a group of patients with both stasis dermatitis and stasis ulcers caused by varicose veins. Of all the various types of skin diseases studied, atopic dermatitis showed the least allergic contact sensitization to neomycin.

In another study of patients with atopic dermatitis, neomycin allergy was found in 1.2 percent of males and 0.0 percent of females. In nonatopic patients, neomycin allergy was found in 3.6 percent of males and 4.4 percent of females (Ref. 38). In the same study, sensitization to other chemicals such as nickel, dichromate, cobalt, rubber, balsam, and benzocaine was also found to be higher in nonatopic patients than in atopic patients.

The Panel concludes that there is evidence showing that patients with the atopic state are less likely to become allergic to topical medications including neomycin sulfate than people with normal skin.

(iii) *Allergic sensitization to neomycin.* Reports in the literature documenting allergic contact dermatitis produced by neomycin are numerous. By March 1975, over 60 English language references dealt with the subject of neomycin sensitivity (allergy) (Ref. 43). The clinical appearance of topical neomycin allergy in many instances is as an aggravation of a preexisting dermatitis, so that the diagnosis is easily missed (Refs. 44 and 45). The true prevalence of neomycin allergy in the United States is unknown. The following studies reflect only the prevalence of neomycin allergy in patients with underlying skin problems such as stasis dermatitis (eczema due to impeded circulation), leg ulcers, and hand eczema.

In the United States, recognition of neomycin dermatitis began in 1952 (Ref. 46). By 1963 there was widespread recognition of neomycin dermatitis, as Epstein and Wenzel stated: "An inquiry among nearly 200 dermatologists in the United States in the fall of 1962 revealed that sensitivity to neomycin is not rare. Some had observed close to 100 cases of sensitivity to neomycin (Ref. 47)." In 1973 a cooperative study in the United States by members of the North American Contact Dermatitis Research Group revealed neomycin sensitivity in 6 percent of 1,200 patients with known contact dermatitis (Ref. 48).

Neomycin sensitivity has also been studied extensively in northern Europe. By 1959 over 240 cases of neomycin sensitization were reported in Helsinki (Refs. 49 and 50). In Denmark, topical neomycin allergy was found in 10 percent of all patients with dermatitis who were patch tested between 1962 and 1964 (Ref. 51). Among 159 patients with positive neomycin patch tests seen between 1963 and 1964, only 115 were able to give a precise account of using a neomycin-containing preparation. In England in 1963, neomycin sensitivity was found in 4 percent of patients with contact dermatitis (Ref. 52).

In 1969 a study by the International Contact Dermatitis Research Group with membership from the United States and several European countries revealed a 3.7 percent prevalence of neomycin allergy among 4,825 patients with contact dermatitis (Ref. 53). The prevalence of neomycin allergy varied from country to country and was thought to reflect varying frequency of consumer exposure to topical neomycin. In the United States, the true prevalence of neomycin allergy remains unknown. The only study testing for neomycin sensitivity in people in the United States without contact dermatitis or other skin problems, demonstrated neomycin sensitivity in 8 percent of 100 people patch tested (Ref. 54).

The apparent prevalence of neomycin sensitivity in recent years probably reflects increasing consumer use of topical neomycin with increased opportunity for sensitization. In the United States, neomycin-containing products have become the most widely used topical antibiotics (Ref. 55). In 1966 Stoltze observed: "The large number of positive reactions to neomycin corresponds to the widespread use of neomycin-containing ointments (neomycin/bacitracin mixtures) during the past 10 years, and during the past 5 years in the form of steroid ointments containing neomycin" (Ref. 56). In addition to being in these ointment and cream products, neomycin has also been present in certain cosmetics and deodorants (Ref. 57).

The type of commercial product containing neomycin sulfate used probably influences the resulting frequency of allergic sensitization to neomycin. In Denmark (Ref. 51) neomycin in ointment vehicles caused 77 percent of the cases of allergic sensitization, while cream, lotions, powders, and eyedrops accounted for only 22 percent of cases. At that time (1968), ointments comprised just under half of the total amount of topical neomycin sold in Denmark. The authors in the above study recommended that neomycin not be prescribed in an ointment vehicle (Ref. 51). In the United States, at the present time, ointments are the predominant neomycin-containing commercial products available in the OTC market (Ref. 58).

The initial development of allergic contact sensitivity to neomycin usually occurs after repeated use of topical medication containing neomycin. Skin conditions commonly predisposing to prolonged use of neomycin include hand eczema, external otitis (inflammation of the external ear canal) (Ref. 59), stasis dermatitis, and stasis leg ulcers associated with varicose veins. The presence of infected dermatitis predisposes patients to develop allergic contact sensitivity to medications (Ref. 55). Positive patch tests to neomycin and other substances are particularly common in patients with stasis dermatitis and stasis leg ulcers (Refs. 60 and 61). In contrast, positive patch tests to neomycin are much less common in patients with atopic dermatitis (Ref. 60).

The internationally accepted concentration of neomycin used in patch testing is 20 percent neomycin sulfate in petrolatum base (Ref. 6). While this concentration is markedly higher than the 0.5 percent concentration of neomycin found in OTC products, it is apparently necessary in order to produce absorption of neomycin through the intact normal skin which is always used in patch testing (Ref. 62). Neomycin is so poorly absorbed through intact skin that no detectable concentrations of neomycin were found in the blood or urine of normal volunteers who were covered with 0.5 percent neomycin ointment for 6 hours (Ref. 63).

The concentration of neomycin used in patch tests has been controversial. Some authorities use 30 to 50 percent (Ref. 55), while others believe that the concentration should be much less than 20 percent (Ref. 64). The Panel recognizes the limitations of this system, but concludes that it is presently the best test system available for identifying allergic skin disease. However, neomycin is very easily absorbed through broken skin damaged by dermatitis, inflammation, or trauma. Some studies have deliberately broken the skin through scratching (scarification) prior to patch testing to assure absorption of neomycin through the barrier layer of skin (Refs. 62 and 65). Other studies have by-passed the barrier layer by injecting neomycin directly into the dermis through the technique of intradermal testing (Refs. 44, 45, 62, and 66). Although intracutaneous injections of 1.0 percent neomycin have been used for testing neomycin allergy in the past (Ref. 44), the Panel concludes that this method is not valid for determining neomycin sensitization. Neomycin has been reported to induce mast-cell degranulation in guinea pigs at the site of injection, with resulting histamine release and development of a dermal papular (hive-like) reaction (Ref. 67). This work has not been repeated in animals nor in humans. The Panel has concluded that this phenomenon and observations concerning it are probably not relevant to neomycin sensitization. Today, intracutaneous testing with 1 percent neomycin is not a usual or customary clinical test.

For a positive neomycin patch test to be considered valid, subsequent application of a commercial product containing neomycin must produce dermatitis in the same individual. Presumably, for absorption of neomycin to have occurred and triggered development of an allergic reaction, a neomycin product must have been applied to skin already damaged by preexisting dermatitis, ulcerations, or traumatic injuries. This may happen inadvertently when a patient previously sensitized to neomycin applies a neomycin-containing product to an area of dermatitis.

The Panel is aware of conflicting medical opinion as to the significance and severity of neomycin sensitization. In spite of the fact that neomycin is a recognized sensitizer, adequate data are not available to predict the sensitization potential of this antibiotic.

The Panel also concluded that a study to determine the sensitizing potential in a random population sample taken from the population at large should also be performed. This should be one of the several adaptations of the Kligman Maximization Test (Ref. 68). Earlier studies of sensitization potential have used limited populations, i.e., restricted in terms of age, sex, and race. The results of this study must be evaluated before neomycin can be considered for Category I. Physicians who favor continued OTC use of neomycin generally believe that the application of neomycin to small cuts and abrasions will most likely not lead to allergic sensitization (Ref. 64). They call attention to the fact that most studies demonstrating significant prevalence of neomycin sensitivity involve patients with prior dermatitis, and they believe that proper package labeling of neomycin products can guard against improper use of neomycin in such conditions. In 1963 Epstein and Wenzel stated: "Proper awareness of the possibility of sensitization, especially in infectious eczemas, appears to us adequate to prevent serious and prolonged disability from neomycin sensitivity (Ref. 47)."

In contrast, physicians who favor removal of neomycin from OTC products believe that neomycin presents an unjustifiably high risk of sensitization to the consuming public, no matter how it is applied. They feel that even if the resulting contact dermatitis in sensitized individuals is mild, and clears rapidly after neomycin is discontinued, the consumer should not be exposed to the resulting discomfort and potential disability. They also point out that neomycin sensitivity occasionally may result in severe reactions, as documented by Kirton and Munro-Ashman in 1965: "Thirty-nine patients said they were worse with neomycin, and occasionally the reaction was so severe that they were admitted to hospitals as emergencies (eight cases). One patient nearly died of exfoliative dermatitis as a result of his sensitivity" (Ref. 69).

Allergic sensitization to neomycin is of further concern due to possible development of cross-sensitization to structurally related chemicals. Cross-sensitization refers to induction of allergic contact dermatitis by one or more closely-related chemicals following initial sensitization to a different chemical of similar structure. Neomycin is one of several structurally-related aminoglycoside antibiotics presently marketed or under investigation for possible future marketing.

Cross-sensitization, as indicated by patch testing, has been well-documented among several types of aminoglycoside antibiotics. In 1958, cross-sensitization between neomycin and streptomycin was found in 8 patients originally sensitized to neomycin (Ref. 65). In 1962 cross-sensitivity between neomycin and paromomycin was found in 97 percent of 29 patients initially sensitized to neomycin (Ref. 70). In the same study, cross-sensitivity between neomycin and kanamycin was found in 58 percent of the 29 patients (Ref. 70). In 1965, cross-sensitivity between neomycin and framycetin was reported in 45 patients (Ref. 69). Cross-sensitivity between neomycin and gentamicin has been demonstrated in two separate studies in 1967 and 1973 (Refs. 71 and 72). The first study found 40 percent cross-sensitization in 100 patients (Ref. 71) while the second study found 55 percent gross-sensitization in 20 patients (Ref. 72). In 1973 cross-sensitization was also demonstrated between neomycin and butirosin in 90 percent of 20 patients (Ref. 72).

The possible implication of the above cross-sensitization (allergic reaction) data is of concern to the Panel. Recognizing the widespread use of topical neomycin, to what extent will induced neomycin allergy preclude future therapy with other potentially life-saving aminoglycoside antibiotics?

The Panel received a submission from a prominent dermatologist (Ref. 73). In the submission were responses from some members of the North American Contact Dermatitis Group to a communication which, regrettably, was based on a misconception of the Panel's belief as to the degree of possible allergic reaction of the general population to neomycin preparations.

At no time did the Panel express a belief that "6% of the population using 0.5% neomycin-containing preparations on minor cuts, abrasions, burns, etc. will get a contact dermatitis" as is stated in the submission.

Each of the respondents to the submission agreed, as does the Panel, that more studies and data are needed. The work of the North American Contact Dermatitis Group (Ref. 48) had been previously scrutinized by the Panel, and the fact that this study was conducted in a group of subjects with allergic skin disease had been noted. Clearly, one is unable to draw inferences applicable to a general population from this study of special patients. It is precisely this lack of prevalence and incidence data for the general population that has led the Panel to conclude that such information is required to accurately assess the risk of neomycin allergy. It is probable that the prevalence of neomycin allergy in the general population will be lower than that reported by the North American Contact Dermatitis Group for allergic patients.

Valid epidemiological studies designed to determine the prevalence of neomycin allergy in the general population are required to quantitate the risk of this ingredient. While, ideally, an incidence study would be most informative, it would probably not be feasible to conduct at a reasonable cost. A prevalence study would be more feasible and not unreasonably expensive. The aim of such a study would be to determine the frequency of allergic reactions to neomycin applied topically. A representative sample of the general population would have to consent to be skin-tested, and age, race, and sex-specific prevalence rates determined. This will give an estimate of the amount of neomycin sensitization currently present in the general population; however, it tells nothing of incidence (number of new cases of neomycin sensitization occurring over time). Furthermore, prevalence is determined by the duration and persistence over time of the allergic reaction. If such allergic reactions are very persistent, prevalence will be higher than if these reactions are of short duration.

Incidence and prevalence are terms that are easily confused; therefore, the Panel has defined them as follows: Incidence is the number of new cases of disease (for example, neomycin allergy disease) occurring in a defined population during a given time period. Incidence is express as a rate:

$$\frac{\text{Numbers of new cases of a disease in a year}}{\text{Numbers of persons in population}} \times K$$

(K=a constant of 10,000 or 100,000); and prevalence is the number of cases of a disease that exist at one point in time in a defined population. This is a cross-sectional measure rather than the longitudinal measure which is the case with incidence. Prevalence is expressed as a rate:

$$\frac{\text{Number of cases of neomycin allergy detected in a defined population as part of a survey conducted at a specified time}}{\text{Numbers of persons in population}} \times K$$

Whether or not "general" population prevalence or incidence figures can be inferred from a prevalence or incidence study depends on the representativeness of the population studied.

(2) *Effectiveness.* Experience with topical use of neomycin ointments, creams, lotions, and aqueous solutions in treating skin infections has been reported in many journals since 1951. Most reports lacked controls, and many lacked adequate bacterial cultures, with results based primarily on undocumented clinical impressions. The following discussion does not include the use of neomycin in combination topical antibiotic products, to be discussed later in this document.

In 1951 Falk and Allende (Ref. 74) used neomycin ointment or aqueous solution in 30 patients with various skin infections, with good results in 15 and moderate results in 14 cases. No controls or cultures were included in the report and no differentiation was made between

results with different bases. In 1952 Kile et al. (Ref. 75) treated 652 patients with assorted skin infections with neomycin cream, ointment, ophthalmic ointment, or wet dressings. Bacterial cultures were done only on 151 patients. Results were reported as good in 233, moderate in 357, and poor in 62 cases. No controls were included in the study. The ointment was thought to be more effective than the cream, although no differentiation between bases was made in reporting results. Forbes (Ref. 76) in 1952 also reported that neomycin ointment was superior to neomycin cream in treating 115 patients with various skin infections. Results were good in 66, moderate in 33, and poor in 16 cases. Bacterial cultures were included for a majority of cases, but no controls were reported in the study. In 1952 Livingood et al. (Ref. 77) reported treating 203 patients with skin infections with neomycin in ointment, aqueous solution, or water miscible base. Results were reported as good in 131, moderate in 33, and poor in 39 cases. Bacterial cultures with in vitro susceptibility studies indicated that neomycin was effective against staphylococci, *Pseudomonas*, and *Proteus* organisms encountered, but not effective against streptococci. Hemolytic streptococci were found in 7 lesions which did not heal. No controls were included in the study, and no differentiation between various bases was made in reporting results.

Forbes (Ref. 78) in 1953 used neomycin lotion to treat 126 patients with skin infections, with results reported as good in 62, moderate in 50, and poor in 14 cases. Cultures were included, showing 81 percent to have pathogenic staphylococci. No controls were included. In the same study, 209 patients with small postoperative electrodessicated wound sites (dehydrated tissue due to high frequency electric current) were treated prophylactically with neomycin lotion to prevent infection, with no infection being encountered.

In 1954 Robinson (Ref. 79) reported the combined experience of 4 dermatologists using topical antibiotic ointments in 5,000 patients with assorted pyodermas. In this general review without statistical data, neomycin was felt to be the topical antibiotic of choice for treating skin infections such as impetigo, ecthyma, and secondarily infected skin diseases. In 1954 Church (Ref. 80) used neomycin ointment and cream to treat 87 cases of skin infection with results reported as good in 50, moderate in 25, and poor in 2 cases. Among impetigo cases, 27 of 45 cleared in the first 7 days. Ointment and cream preparations of neomycin were felt to be equally effective in clearing infections, but no differentiation between bases was made in reporting results. All cases of infection were cultured before treatment, but no controls were included in the study.

In 1956 Forbes and King (Ref. 81) used neomycin lotion to treat miliaria ("prickly heat") in infants and young adults, with good results in 30 and moderate results in 13 cases. Use of the vehicle alone in five patients did not produce clearing. Lyons and Hunt (Ref. 82) treated 91 cases of miliaria rubra in a double-blinded study comparing neomycin lotion and lotion base alone. Both groups improved objectively and subjectively in 48 hours, but the clearing time of skin lesions was approximately 2 days shorter in the neomycin-treated group. Although this double-blinded study showed apparent superiority of neomycin over lotion base alone, the significance of this finding is difficult to interpret. The etiology of prickly heat is unknown and may, or may not, be related to bacterial infection. The Panel therefore concludes that this study is not relevant to the OTC application of neomycin to small cuts, wounds, burns, or abrasions.

In 1967 Farah et al. (Ref. 83) used neomycin ointment to treat 44 patients with superficial skin infections. Results were good in 22, moderate in 16, and poor in 6 cases. In the same study, gentamicin cream was used in treating skin infections in 84 patients. After 5 days of treatment, good results were seen in 71.4 percent of gentamicin-treated cases and 50 percent of neomycin-treated cases. With longer treatment periods, good results were almost identical in the two groups, with clearing of 86 percent of neomycin-treated group and 88 percent of gentamicin-treated cases. Cultures with antibiotic susceptibility testing were included, but no control ointment or cream was used. Keeping the above study in mind, the 1974 report of Zaynoun et al. (Ref. 84) becomes noteworthy, in which gentamicin cream and placebo cream were used in a double-blinded manner to treat 46 patients with skin infections. Each patient used hexachlorophene scrubs in addition to either gentamicin cream 0.1 percent or placebo cream. After 1 week, good results were seen in 52 percent of the gentamicin-treated group and 48 percent of the placebo-treated group, with no statistical difference between the two treatments. Neither treatment totally prevented the development of new lesions. Bacterial cultures of all cases showed that all bacteria recovered were sensitive to gentamicin. The authors concluded that topical antibiotics should not be used to treat skin infections since they are frequently ineffective. Although gentamicin is not currently under review for OTC topical use, the Panel concludes that the above study is relevant to the present report regarding the use of topical antibiotics in general. It is one of the few controlled studies which compares the use of a topical antibiotic to use of its base alone. The Panel concludes that the study raises serious questions about the clinical effectiveness of topical antibiotics in general for the treatment of superficial skin infections.

In 1951 Reiss and Pulaski (Ref. 85) studied the effect of neomycin ointment on 50 infected burns healing with granulation. Control burns, presumably on the same patients, were treated in a double-blinded manner with plain petrolatum. Cultures showed no alteration in bacterial flora of either group after neomycin treatment despite sensitivity of 80 percent of cultured organisms to neomycin. Formation of pus was the same in neomycin-treated burns as in control burns treated with petrolatum. No difference in healing time was noted subjectively between the two groups, although no objective appraisal of healing time was given. It was concluded that neomycin ointment did not eradicate pathogenic organisms any better, nor promote healing of granulating burns any faster, than did the placebo ointment. The Panel concludes that this carefully controlled study raises serious doubts about the effectiveness of neomycin ointment compared to the ointment base alone. The study also raises questions about the necessity of eliminating pathogenic bacteria from superficial wounds to promote healing.

Neomycin aqueous solution has been used in treating orthopedic surgical wounds. In 1968 Nachamie et al. (Ref. 86) reported a controlled study performed over 28 months in which wounds were irrigated with either saline solution alone or neomycin solution 0.1 percent plus saline solution. During each alternate month, neomycin was used in every surgical wound. Over the 28-month period neomycin was used in 219 of 466 surgical cases. No statistically significant difference in the incidence periods, with infections developing in 5.1 percent of neomycin-treated wounds and 4.4 percent of control wounds. Although the wounds in the study are very different from superficial skin wounds and the aqueous base is not under consideration for OTC use, the Panel concludes that this controlled study is relevant to the present review as it raises questions about the clinical effectiveness of topical neomycin sulfate when compared to its vehicle alone.

(3) *Dosage.* Topical ointment dosage, for both adults and children, should be not less than 5 mg neomycin sulfate per gm of finished ointment dosage form. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for skin wound antibiotic ingredients. (See part IV. paragraph B.1. above—Category I Labeling). In addition, the Panel recommends the following specific labeling: "Do not use for burns, diaper rash or heat rash which cover large areas of the body."

(5) *Evaluation.* The Panel concludes that neomycin requires controlled clinical evaluation to establish prophylactic and therapeutic effectiveness. In addition, further safety data are required to evaluate allergic sensitization and bacteria resistance. (i) *Allergic sensitization.* The Panel concludes that studies should be performed to determine the incidence and/or prevalence of neomycin sensitization in the population at large. Considering the potential benefit-to-risk, and considering the type of reaction resulting from this type of sensitization, the Panel recommends that if more than 0.1 percent of the population at large is

found to be sensitized to neomycin, it should be moved to Category II for reasons of safety. If less than 0.1 percent of the population at large is sensitized to neomycin, the Panel recommends that neomycin be placed in Category I for safety.

(ii) *Clinical effectiveness.* The Panel concludes that there are insufficient controlled data presently available to evaluate the clinical effectiveness of topical neomycin sulfate. There were virtually no controlled studies documenting that any formulated topical product containing neomycin sulfate as the only active ingredient was statistically any better than the product vehicle (base) alone. To the contrary, the controlled studies by Reiss and Pulaski (Ref. 85) and Nachamie et al. (Ref. 86) suggested that at least some topical neomycin sulfate preparations were not superior to their vehicles alone.

The Panel recognizes that some evidence from uncontrolled studies presented above suggests that topical neomycin sulfate may be helpful in preventing and treating superficial skin infections. The Panel also recognizes that differences of opinion exist as to the relative merits of these studies, and appreciates the many difficulties inherent in attempting to scientifically document clinical effectiveness. However, the Panel was not willing to accept uncontrolled clinical studies as proof of clinical effectiveness, even if adequate bacterial cultures are included in the study.

The Panel concludes that further double-blinded, randomized, controlled clinical trials are necessary to evaluate the clinical effectiveness of neomycin sulfate. If controlled studies indicate that neomycin ointment or cream is significantly more effective than the vehicle alone in preventing and treating infections in superficial skin wounds, the Panel concludes that neomycin sulfate should be moved to Category I for effectiveness.

(iii) *Bacterial resistance.* The Panel is concerned that a continued widespread use of neomycin sulfate on superficial skin conditions may result in an increasing antibiotic resistance of the skin staphylococci in the general population. This could have a deleterious effect in systemic staphylococcal infections where the organisms are already resistant to neomycin and cross-resistant to the other aminoglycoside antibiotics which could be used for the more serious systemic infections of life-threatening type.

The previous epidemiologic history of neomycin resistance illustrates that changes in resistance patterns do occur uniformly, and that a long period of time may be observed in which only sensitive strains are found in the face of widespread antibiotic use. These findings in no way guarantee freedom from the widespread development of resistant strains at a future date. Enough evidence has accumulated in the last 25 years to predict that with increasing use of any antibiotic, particularly on the body surface with the interaction with staphylococci, the resistance pattern will probably follow that of neomycin. Therefore the Panel concludes that continuing, on-going analyses of the susceptibility profile are required when antibiotics for topical use are proposed. Refer to in vitro testing as described in the guidelines elsewhere in this document. (See part VI. paragraph B.2.a. below—In vitro testing).

In summary, the Panel concludes that neomycin sulfate may be reclassified from Category III to Category I only if all of the following criteria are satisfied:

(a) Sensitization to neomycin is found to occur in no more than 0.1 percent of the population at large in a properly designed prevalence study of sufficient size of a representative sample of the general population.

(b) Updated bacteriologic surveys indicate that the susceptibility of staphylococci isolated from lesions in the general population do not show rapidly increasing resistance to neomycin or related aminoglycoside antibiotics.

(c) Controlled clinical studies indicate that neomycin sulfate used topically is significantly more effective than the vehicle alone in preventing and/or treating infections in superficial skin wounds.

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d. *Polymyxin B sulfate.* The Panel concludes that polymyxin B sulfate is safe when in the concentration used as a skin wound antibiotic for application on small areas of the body. However, there are insufficient effectiveness data to permit final classification as a skin wound antibiotic. It should be fully understood that the Panel concludes that polymyxin B sulfate should not be used alone as a single antibiotic ingredient in a topical preparation for skin wounds. Since most infections of the skin are caused by gram-positive organisms, and since polymyxin B is not effective against gram-positive organisms, it is the judgment of the Panel that if it were to be used alone in topical antibiotic preparations it could not be generally recognized as effective because of its limited spectrum. In an acceptable combination product, however, polymyzin B sulfate could be included to significantly broaden the antibacterial spectrum and thereby improve the potential effectiveness of such a combination product.

The five polymyxins—A, B, C, D, and E—are produced by the soil baeterium, *Bacillus polymyxa* (British *B. aerosporus*). They were discovered in 1947 in both England and the United States. Due to the toxicity of the others, polymyxin B has been the one generally used in the United States and the only one certified. Polymyxin E (colistin) has been more widely used in Britain (Ref. 1).

Chemically, the polymyxins are polypeptides with molecular weights of about 1,100. Polymyxin B, as the hydrochloride or sulfate, is water-soluble and is stable at 60° C for 1 hour. Commercial preparations of polymyxins B and E are 65 to 75 percent pure. The unit of polymyxin, based on a theoretical potency of 10,000 units/mg of pure drug, is 10 units/mcg (Ref. 1).

The polymyxins are active against gram-negative rods but are usually not active against Proteus species. Polymyxins are strongly bactericidal. Since their action is on the bacterial cell membrane with subsequent disruption of osmotic properties, the increase in permeability leads to escape of large molecules essential to cellular functions, ultimately causing bacterial cell death. The mode of action is cell wall disruption, increasing bacterial absorption of the antibiotic. The action is bactericidal at all levels of antibiotic and resembles that of chemical disinfectants. There is some evidence

that its activity is inhibited by serum (Ref. 2).

The polymyxins are strongly protein bound. They do not penetrate the cell wall and are most effective if high levels of drug are in direct contact with gram-negative cells and do not have to penetrate a tissue barrier. Polymyxin at the tissue site is strongly absorbed by cell debris and by purulent material (Ref. 1).

Five mcg/ml of polymyxin is considered to be active against *Aerobacter, Klebsiella* and *Pseudomonas*. Resistant strains do occur.

Polymyxin activity is selective against gram-negative organisms including: *Escherichia* and *Enterobacter*. Against *Pseudomonas aeruginosa*, the polymyxins are more effective by weight in vitro than any other antibiotic. Most strains are inhibited by 8 mcg/ml or less of Polymyxin B or E. *Neisseria, Proteus*, and *Brucella* are resistant. *Shigella, Salmonella*, and *Hemophilus* may be sensitive in vitro, but no evidence of clinical effectiveness has been produced. Polymyxins are not active against gram-positive organisms.

There is some evidence of synergism with the tetracyclines and chloramphenicol (Ref. 1).

Resistance to polymyxins develops slowly. Polymyxins B and E show complete cross-resistance (Ref. 1).

The polymyxins should be considered as active against only gram-negative organisms such as the coliforms and Pseudomonas, and have no activity against the gram-positive organisms such as the micrococci, staphylococci or streptococci found on the skin surfaces as transients, residents, or pathogens.

(1) *Safety*. Though there is very little basic toxicological data available on the polymyxins, it can be stated that the acute toxicity of the several polymyxins appears to be similar. Much of the data concerning the toxicology of the polymyxins have been detailed in the monograph by Jawetz (Ref. 1) and the chapter by Manten (Ref. 3). The following summary is extracted from these sources.

When administered intravenously to mice, the LD_{50} of polymyxin B is approximately 6.1 mg/kg with death resulting in a few minutes from respiratory failure (Ref. 1). In fact, polymyxins are known to have a neuromuscular blockage effect in models designed to test such systems (Ref. 3). When given by the intraperitoneal route, the acute LD_{50} in mice is 12.1 mg/kg and is 82.5 mg/kg by subcutaneous injection. Symptoms leading to respiratory failure include weakness of limbs, shivering, and convulsion, all indicating a neurotoxic effect (Ref. 1).

In dogs, the intravenous administration of 1 to 3 mg/kg of polymyxin B resulted in a temporary depression of kidney function. Doses of 2.5 mg/kg given intramuscularly daily for 2 to 6 weeks in dogs resulted in transient depression of tubular (kidney) function (Ref. 1).

Topical application of polymyxin in low concentration (0.1 percent) apparently does not cause irritation to mucous membranes or granulating surfaces. Polymyxin is reported to be poorly absorbed after oral administration (Ref. 1). One report (Ref. 4) stated that no significant blood or urine levels could be obtained after topical application to large burns. Polymyxin blood levels of 15 mcg/kg in human patients have resulted in marked nitrogen retention. Jawetz and Coleman (Ref. 5) also found that patients whose serum levels were between 1 and 4 mcg/ml showed no alteration of nonprotein nitrogen. Since the major route of elimination is via the kidney, it has been suggested that in patients with preexisting impairment of renal function, doses of 1.5 mg/kg/day or less may result in additional depressed kidney function.

In view of the above summary, it is the judgment of the Panel that when polymyxin B sulfate is applied to intact skin, there is no evidence of a potential hazard from its use. When polymyxin B sulfate is applied to large areas of broken, denuded, or diseased skin, there are less firm data on which to base a sound scientific judgment concerning potential toxicity. In fact, there is only the one report (Ref. 4) that indicated polymyxin B was not absorbed to a significant degree from large burn areas.

It is the view of the Panel that when polymyxin B sulfate is applied to small cuts, abraisons, or burned areas, the amount of polymyxin B sulfate that could be expected to be absorbed into systemic circulation is far below the level that has been demonstrated to cause signs of toxicity in animals. The Panel feels that is no need for further basic toxicological studies on the polymyxins when formulations containing them are applied to small areas of broken skin. There would be concern for safety if large areas of broken skin were exposed to continued medication with ploymyxin B sulfate and/or if large areas of skin were occluded.

POLYMYXIN ALLERGY

The Panel has reviewed the literature in regard to the allergenicity of topical polymyxins. The literature does not indicate that polymyxin B sulfate is a significant cause of allergic skin disease. Members of the North American Contact Dermatitis Group, polled informally, supported this judgment (Ref. 6). While there are occasional, isolated case reports of possible allergy to topical polymyxin B, the reported prevalence is so small as to be considered inconsequential.

(2) *Effectiveness*. Clinical use of topical preparations containing polymyxin B as a single antibiotic has not been extensive, with most reports dating from 1949 to 1952 (Refs. 4 through 10). Polymyxin B sulfate as a single antibiotic agent has been used in solutions, sprays, creams, ointments, and jelly bases.

In 1949 Pulaski et al. (Ref. 7) in a preliminary, uncontrolled report indicated that polymyxin B, 1.0 percent in salt solution or carbowax base, was effective in eradicating *Pseudomonas aeruginosa* from infected granulating wounds if devitalized tissue were not present. In 1951 Jackson et al. (Ref. 4) used polymyxin E in a controlled study to treat burns infected with Pseudomonas. Alternate patients received therapy consisting of combinations of polymyxin E cream 0.1 percent and polymyxin E spray solution 0.1 percent or placebo cream and placebo spray. Polymyxin E significantly decreased the number of positive culture sites after 3 to 7 days. In the same study, prophylactic use of polymyxin spray and cream on patients in burn wards resulted in marked reduction of new Pseudomonas infections, with infection developing in only 7 percent of polymyxin treated patients in contrast to 24 percent of control patients. Use of polymyxin also resulted in fewer skin graft failures and shortened healing times of skin grafts by approximately 3 weeks. It was concluded by the authors that polmyxin 0.1 percent in cream base or spray can protect most burns against infection by Pseudomonas (Ref. 4). No mention was made of using polymyxin in an ointment base, which is the only form in which polymyxin is currently marketed OTC.

In 1952 Jawetz and Coleman (Ref. 5) used polymyxin solution 0.5–1.0 mg/ml to treat nine cases of surgical wound infections and four cases of chronic otitis media (infected ears). Continuous wet dressings and frequent instillation of polymyxin solution into wounds or ears inflamed with *Pseudomonas* resulted in prompt healing in most cases. While this study seemed promising, it had no controls and only a very small number of cases. No mention was made of using polymyxin in either ointment or cream base.

In 1952 Gastineau and Florestano (Ref. 9) used polymyxin ointment containing 8,000 units per gm of base experimentally in rabbits to treat 1.5 centimeter-circular wounds infected with either single cultures of *Proteus, Pseudomonas, Staphylococcus aureus*, or B-hemolytic streptococci, or mixed cultures of *Pseudomonas* and *Staphylococcus aureus*. The ointment eradicated *Proteus* and *Pseudomonas* but not staphylococci or streptococci. When polymyxin was combined with bacitracin 400 units per gm of ointment base, all bacteria appeared to be removed from the wounds. No wounds were treated with ointment base alone.

In 1961 Mulla (Ref. 10) in a double-blinded controlled study attempted to evaluate the effectiveness of topical polymyxin jelly in preventing urinary tract infections associated with bladder catheterization. Either control jelly or polymyxin jelly containing 5,000 units of polymyxin per gm of base was applied to the urethra and catheter tip prior to catheterization, and every 6 hours while the catheter was in place. Although fewer cases of bladder infection and bacteria in the urine occurred in the polymyxin-treated group than in the control group, the difference was not significant. The study considered only polymyxin in jelly base, which is not available commercially, and is not considered relevant by

the Panel for evaluation of currently used OTC topical antibiotics.

(3) Dosage. Topical ointment dosage, for both adults and children, should be 4,000 to 5,000 units of polymyxin B per gm of finished ointment dosage form when used in combination. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface area of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(4) Labeling. The Panel recommends the Category I labeling for skin wound antibiotic ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) Evaluation. The Panel concludes that polymyxin B requires controlled clinical evaluation to establish prophylactic and therapeutic effectiveness. Polymyxin B sulfate appears to be a safe antibiotic for OTC use, with no evidence that toxicity would result from use of polymyxin products on small wounds. The Panel further concludes that polymyxin B surfate should never be used as the sole active ingredient of a topical antibiotic product since its spectrum of activity is limited to gram-negative bacteria not frequently found in superficial skin infections. The Panel urges that further investigative work on polymyxin B sulfate be undertaken to show effectiveness when in a combination product. If such prophylactic and/or therapeutic effectiveness of polymyxin B is demonstrated in controlled clinical trials involving minor skin wounds, polymyxin B sulfate should be reclassified as Category I.

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e. *Tetracyclines (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride)*. The Panel concludes that while the tetracyclines are safe in the concentrations used as a skin wound antibiotic for application on small areas of the body, there are insufficient effectiveness data to permit final classification as skin wound antibiotics.

The first of the tetracyclines was discovered in 1948. A series of antibiotics isolated from *Streptomyces* species have been referred to as the tetracyclines or the tetracycline group. This refers to their chemical structure consisting of four, six-membered (cyclic) rings having slight modifications on the rings with chloro- or oxy-groupings. Thus the names tetracycline, chlortetracycline and oxytetracycline have been developed. The change or loss of the groupings can modify their chemical activity and their antibiotic activity.

They are yellow, crystalline, amphoteric chemicals. Chlortetracycline is very unstable at alkaline or neutral pH, while oxytetracycline and tetracycline are both stable. Chlortetracycline activity is lost overnight in broth at pH 7.4. All of these antibiotics have a broad spectrum activity against gram-positive and gram-negative organisms *Rickettsia, Chlamydia, Treponema,* and *Mycobacterium*. The higher fungi are resistent except that *Actinomyces* show susceptibility. Chlortetracycline is most active against the gram-positive cocci. Oxytetracycline shows some activity against *Pseudomonas* and *Proteus*. Resistance has developed in the coliforms, staphylococci, streptococci, peneumococci, and the gas-gangrene clostridia.

Chemically, there are minor variations in their basic structures and they can be further modified, for example, to increase solubility. Stability varies among members of the group.

They are considered bacteriostatic and their mode of action is interference with protein synthesis in bacterial cells (Ref. 1). Specifically, they inhibit metabolism by blocking attachment of aminoacyl transfer RNA to ribosomes. The tetracyclines are also active chelating compounds, forming unions with divalent and trivalent cations, and can thereby interfere with enzymes that require such cations as cofactors. They activity also appears to interfere with the phosphorylation of glucose.

A wide antibacterial spectrum is demonstrated by all of the analogues and includes activity against many gram-positive and gram-negative organisms. They are active against the B-hemolytic streptococci, *Escherichia coli*, meningococci and gonococci and *Hemophilus* species. However, most *Proteus* and *Pseudomonas* species are resistant.

Resistance to these antibiotics has been reported in many strains of staphylococci and streptococci and a few strains of pneumococci, salmonellae, shigellae, and *Escherichia coli*. It often develops rapidly in organisms of the *Klebsiella/Aerobacter/Enterobacter* group and *Escherichia coli*. Cross-resistance is usually complete, but there are some exceptions.

(1) Safety. When the tetracyclines are administered orally or parenterally in large doses, local tissue irritation may occur (Ref. 1). Thrombophlebitis may occur if a single vein is used for repeated infusions (Ref. 1). Large intravenous infusions of tetracycline have induced liver damage, which is believed to result from serum levels of tetracycline exceeding 16 mcg/ml (Ref. 2). Liver damage is a special hazard in pregnant women following large oral or parenteral doses.

Systemic tetracycline therapy when administered to pregnant women or children may result in yellowish brown discoloration of the children's teeth. Severity of the discoloration increases with increased dosage and prolonged administration (Ref. 1).

In view of the long history of oral administration of tetracycline to millions of patients for conditions such as acne vulgaris, upper respiratory infections, and other infectious diseases with minimal toxicity or side effects, the Panel concludes that no toxicological hazards would result from topical application of tetracycline hydrochloride to small wounds, abrasions, burn or skin infections. Therefore, further toxicological examination of tetracycline hydrochloride is unnecessary.

TETRACYCLINE ALLERGY

Tetracyclines applied to the skin have been considered harmless, based on the scarcity of reports of induced eczematous reaction of either the primary irritant or sensitization type. Occasional cases of contact dermatitis of the mouth from use of tetracycline lozenges have been reported, possibly induced by coloring or flavoring agents (Ref. 3). Transitory yellowish discoloration of the tongue has also occurred following systemic tetracycline therapy, but this is not an allergic reaction.

Cases of allergic contact dermatitis following use of topical tetracycline creams or ointments may result from sensitivity to parabens or other preservatives, or to azo dyes, rather than to the tetracycline itself. Dohn in 1960 (Ref. 4) comprehensively discussed the problem of contact dermatitis from topically applied tetracycline. A more recent paper by Bojs and Moller (Ref. 5) reports three cases of sensitivity to topical tetracycline with cross reactions between oxytetracycline, tetracycline, and methacycline. With only a few reports available for review, even after many years of consumer use, the Panel concluded that allergic sensitization to topically applied tetracycline is not a significant problem.

(2) Effectiveness. Tetracycline ointments were used extensively in uncontrolled clinical trials during the early 1950's. Three types of tetracycline ointments were evaluated: Chlortetracycline hydrochloride ointment, oxytetracycline hydrochloride ointment, and tetracycline hydrochloride ointment. In each oint-

ment the concentration of tetracycline was 3 percent.

(i) *Chlortetracycline hydrochloride.* The use of chlortetracycline hydrochloride ointment in over 900 patients is documented in 9 papers appearing between 1950 and 1952 (Refs. 6 through 14). Robinson and Robinson (Ref. 6) treated 304 patients with a wide variety of primary skin infections and secondarily infected skin diseases. Good results were reported in 270 patients, including 59 cases of impetigo, which cleared in 3 to 21 days. No cultures or controls were included in this study. In 1952 Sawicky et al. (Ref. 7) briefly reported treatment of 170 similar cases. Although all impetigo cases cleared within 7 days, improvement occurred in less than 50 percent of all other cases treated. No cultures or controls were included in the report. Solomons (Ref. 8) in 1951 treated 144 patients, with good results in 116 patients, including 53 of 55 cases of impetigo. Although many cultures were performed in this study, no controls were included and the numbers of each type of infection treated were too small for statistical analysis. Jordon (Ref. 9) in 1952 reported treatment of 143 cases of impetigo, ecthyma, folliculitis, and external ear infection with chlortetracycyline ointment. Good results occurred in 129 patients, including 78 of 81 cases of impetigo which healed in an average time of 6 days. No cultures or controls were included in this study. In 1950 Hollander and Hardy (Ref. 10) used chlortetracycline ointment to treat 79 cases of skin infection, with good results in 60 patients. They also treated 57 minor surgical wounds prophylactically with chlortetracycline ointment, with good healing in all cases. No cultures or controls were included in the report. Also in 1950, Siegel and Schantz (Ref. 13) treated 50 patients with various acute and chronic skin infections. Results were good in 40 cases, including 10 cases of impetigo, and moderate in 9 cases. No cultures or controls were included.

In 1951 and 1952 chlortetracycline ointment was used to treat tropical ulcers in Africa by Ampofo and Findlay (Ref. 11) and Lasbrey (Ref. 12). These ulcers contained many types of microorganisms, including spirochetes, fusiform bacilli, and cocci. Most ulcers became less painful within 48 hours, and many ulcers completely healed within 2 weeks. Frequent cultures revealed disappearance of organisms from ulcers in 3 to 5 days. These two studies stood out as the only reports using chlortetracycline onitment in which cultures were consistently performed. However, no controls were included in either report. A single case report of sycosis vulgaris (beard folliculitis) by Saunders (Ref. 14) included a culture positive for *Staphylococcus aureus*, with dramatic clearing of facial pustules previously unresponsive to treatment. However, no control medication was included in the study, and one case cannot be regarded as statistically significant.

(ii) *Oxytetracycline hydrochloride.* Oxytetracycline hydrochloride ointment was used to treat over 2,600 patients between 1951 and 1955, as reported in six papers (Refs. 15 through 20). In a very small, uncontrolled study in 1952 Ampofo (Ref. 15) treated six tropical ulcers of the legs and feet with healing of all ulcers in an average time of 4 weeks. In a much larger study in 1953, Wright and Tschan (Ref. 16) treated 391 patients having superficial infections with oxytetracycline ointment. Good results occurred in 310 patients, including 82 of 90 cases of impetigo, which cleared within 7 days. In the same study, healing without infection occurred in 244 cases of postoperative minor skin wounds treated prophylactically with oxytetracycline ointment. No cultures or controls were included in this study.

In 1952 Reiss (Ref. 17) used oxytetracycline ointment to treat 55 patients with assorted skin infections. Good results were reported for impetigo and beard folliculitis, but not for external ear infections. In five paired-comparison studies on the face involving three cases of facial impetigo and two cases of beard folliculitis, the side treated with oxytetracycline ointment improved somewhat faster than the opposite side treated with either iodochlorhydroxyquin or ammoniated mercury ointments. Although these controlled studies were attempted, their number was too small to be significant and no attempt was made to compare the effect of oxytetracycline ointment to the ointment base alone.

Robinson et al. (Ref. 18) in 1953 reported the use of oxytetracycline ointment in 728 patients with various skin infections and secondarily infected skin diseases. Results were reported as good in 291 and moderate in 228 cases. Impetigo cleared in 3 to 12 days in 105 of 122 cases. No cultures or controls were included in this study. In 1955 Robinson (Ref. 19) reported a similar study with 1,016 patients with various skin infections with good results in 489 patients, including 165 of 191 impetigo cases. Moderate improvement was noted in an additional 379 cases. No cultures or controls were included in the report.

With the exception of the Ampofo study (Ref. 15), no bacterial cultures were documented in the above large clinical studies. Controls were also lacking with the exception of the paired-comparison studies attempted in five patients by Reiss (Ref. 17). In 1951 Reiss and Pulaski (Ref. 20) performed the only study with oxytetracycline ointment which was double blinded and well controlled. Using hospitalized patients with granulating wounds produced by penetrating missiles, the effect of oxytetracycline hydrochloride ointment on healing was compared with that of colored petrolatum. In 30 wounds treated with oxytetracycline hydrochloride ointment, susceptible organisms were eliminated in 24 to 72 hours, whereas in 20 control wounds treated with petrolatum the bacterial flora was unchanged. Although no objective appraisal of healing time was given, no subjective difference in healing time was observed between the 2 groups, despite elimination of pathogenic bacteria in only one group. The conclusion of the authors was that contamination of granulating wounds with common pathogenic bacteria did not significantly delay wound repair. The Panel concludes that this carefully controlled study raises doubts about the effectiveness of oxytetracycline ointment compared to the ointment base alone. The study also raises questions about the significance of the bacterial loads with particular reference to the numbers in relation to superficial wound repair. Although bacteria were apparently eliminated by the antibiotic ointment, healing time of the wound was obviously not shortened.

(iii) *Tetracycline hydrochloride.* The use of tetracycline hydrochloride ointment was documented mainly in 1955 in studies by Welsh and Ede (Ref. 21) and Robinson et al. (Ref. 22). Welsh and Ede reported complete clearing of various pyodermas in 156 of 160 patients with various skin infections. However, their results were difficult to interpret due to concurrent treatment with other agents such as systemic antibiotics and radiation therapy. No cultures or controls were included in the study. Robinson et al. (Ref. 22) treated 923 patients with various skin infections with good results in 421 and moderate results in 343 patients. Although cultures were performed in 100 cases, no controls were included. In a small study an investigator (Ref. 23) treated 13 cases of chronic beard folliculitis with tetracycline ointment, with improvement of all cases in 3 to 7 days. When treatment was stopped, the disease promptly recurred. No cultures or controls were included in the study.

(3) *Dosage.* Topical ointment dosage, for both adults and children, should be not less than 1 mg of chlortetracycline hydrochloride per gm of finished dosage form, and not less than 15 mg of tetracycline hydrochloride per gm of finished ointment dosage form. The amount applied should be sufficient to cover the affected area with a thin layer, not more than 0.5 gm (an amount equal to the surface of the tip of a finger), 1 to 3 times daily with no maximum daily dosage.

(4) *Labeling.* The Panel recommends the Category I labeling for skin wound antibiotic ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

(5) *Evaluation.* In summary, the Panel concludes that tetracycline hydrochloride requires controlled clinical evaluation to establish prophylactic and therapeutic effectiveness. Tetracycline hydrochloride appears to be a safe antibiotic for OTC use, with no evidence of either toxicity or sensitization hazards resulting from use on small areas of infected skin.

Some evidence based on clinical impressions presented above suggests that tetracycline hydrochloride ointment may be helpful in treating superficial skin infections. However, no controlled studies with statistically significant numbers of cases were presented to the Panel showing that tetracycline hydrochloride ointment was therapeutically superior to its ointment base alone in treating superficial skin infections. The only well-

controlled, double-blinded study by Reiss and Pulaski (Ref. 20) suggested that tetracycline hydrochloride ointment and ointment base alone (petrolatum) were of equal therapeutic effectiveness when applied to granulating wounds.

The Panel concludes that if controlled studies indicate that tetracycline hydrochloride ointment is more effective than ointment base alone in preventing and treating infections in superficial skin wounds, tetracycline hydrochloride should be reclassified as Category I. The Panel would also encourage controlled studies with the dosage forms such as creams for possible Category I status.

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V. PRODUCTS COMBINING MULTIPLE TOPICAL ANTIBIOTIC INGREDIENTS

A. GENERAL DISCUSSION

1. *Regulations.* a. The Panel requested an industry task force to survey all the available literature dealing with effectiveness of topical antibiotics. This group not only assembled such data, but in addition, presented very helpful summaries. This data has since been published (Ref. 1).

b. The Panel has followed the OTC drug review regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate direction for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

c. The Panel concludes that, as a general principle, the fewer the ingredients, the safer and more rational the therapy. The Panel also concludes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

d. The Panel concludes that OTC drugs should contain only such inactive ingredients as are necessary for pharmaceutical formulation. These inactive ingredients should be clearly stated on the label as inactive ingredients.

REFERENCE

(1) Anderson, V., "Over-the-Counter Topical Antibiotic Products: Data on Safety and Efficacy," *Supplement to International Journal of Dermatology*, 15:1–118, 1976.

2. *Requirement of significant contribution.* The Panel has determined that each claimed active ingredient in the combination must make a significant contribution to the claimed effect. The only rationale for the combination of antibiotic ingredients for topical application is to significantly broaden the antimicrobial spectrum or compensate for difference in resistance. The Panel concluded that where a combination product is to be permitted, as discussed below, it is sufficient to demonstrate in well-controlled in vitro studies that each of the ingredients makes a significant contribution toward broadening the antimicrobial spectrum. The Panel recognizes that adequate technology does not exist at this time for establishing the optimal concentration of antibiotic in a topical preparation. However, it is desirable that attention be directed toward such a goal.

3. *Single active ingredients.* It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions. However, because many of the antibiotics reviewed have limited antimicrobial spectra, there is often a legitimate need for these claims of products to combine topical antibiotic ingredients to broaden the spectrum. However, these combinations must be within certain limits to be discussed below.

4. *Active ingredients not reviewed by the Panel.* Each claimed active antibiotic ingredient in a combination product must be an ingredient that has been reviewed by the Panel. If a product contains an active antibiotic ingredient that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient; i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by FDA is required before a product containing such an antibiotic ingredient may be marketed.

5. *Antibiotic ingredients combined with nonantibiotics.* If a product contains a generally recognized safe and effective antibiotic ingredient (Category I), it may be combined with nonantibiotic ingredients provided:

a. The antibiotic ingredient remains generally recognized as safe and effective.

b. The nonantibiotic ingredient has been determined to be generally recognized as safe and effective by the appropriate OTC drug advisory panel.

c. The labeling indicates the intended pharmacologic effect(s) of all active ingredients.

d. The combination provides rational concurrent therapy for a significant portion of the target population.

No combinations of antibiotics and nonantibiotics were submitted or reviewed by the Panel. However, it is entirely conceivable that certain nonantibiotic ingredients such as corticosteroids, judged by another Panel to be generally recognized as safe and effective (Category I), could be combined with topical antibiotics. While such a combination would have to be properly evaluated, it would be rational for the purpose of reducing signs of inflammation. However, the Panel considers the combining of an-

tibiotic and nonantibiotic ingredients to be irrational and without scientific basis and merely for the purpose of marketing advantage, particularly if the combination might result in a potentially serious health hazard. For example, combinations of antibiotics with local anesthetics (particularly those with a similar chemical structure to benzocaine) would not be safe or rational because these ingredients might mask symptoms of a worsening infection due to a pathogen's resistance to a particular topical antibiotic. Without pain because of action of a local anesthetic, the patient would be lulled into a false sense of security, believing the wound was healing when in fact the infection was actually spreading.

6. *Antibiotic ingredient combined with not more than two other antibiotic ingredients.* A Category I antibiotic ingredient can be combined with not more than two other Category I antibiotics provided:

a. The antibiotic ingredients all remain generally recognized as safe and effective.

b. The combination provides rational concurrent therapy for a significant portion of the target population. The Panel believes that if the addition of a second or third topical antibiotic ingredient to the product significantly increases the antimicrobial spectrum of the combination product, then the new ingredients have contributed to the combination. In addition, the increased antimicrobial spectrum must be relevant to the intended claim.

Conversely, if the addition of the second or third antibiotic to a combination does not significantly increase the spectrum, or the increased antimicrobial spectrum has no relevance to the intended claim, then those ingredients cannot be considered to have contributed to the combination. An example of the latter situation might occur if the addition of the second or third antibiotic expanded the combination's antimicrobial spectrum, but there was little likelihood the new microorganisms intended to be killed would be found either in the normal microbial flora of the skin or in the microbial flora of small wounds.

7. *Review of submitted combination products.* The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of September 7, 1973 (38 FR 24391) and certain other possible combinations based on the antimicrobial spectrum of single ingredients. The Panel recognizes that other combination products may be in the marketplace, but it has either no knowledge of such products or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Acordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel, be evaluated through the new drug procedures or be the subject of an appropriate petition to the Commissioner to review or amend the OTC topical antibiotic monograph.

B. CLASSIFICATION OF COMBINATION PRODUCTS

1. *Criteria for determining Category I combination products.* To qualify as a Category I combination product, i.e., one that is generally recognized as safe and effective and not misbranded, each of the following conditions must be met:

a. Each active antibiotic and claim in the combination product is Category I, as set forth elsewhere in this document for single topical antibiotic ingredients and claims.

b. The active antibiotic ingredients are combined on the basis of broadening the relevant antimicrobial spectrum. (The Panel wishes to reemphasize its previous conclusion that the narrow antimicrobial spectrum of polymyxin makes it imperative that this ingredient only be used in combination with at least one other antibiotic ingredient.)

2. *Combinations allowable as Category I.* Based on the combinations submitted and discussed below in this document, and the above criteria for Category I combinations, the Panel places all presently marketed combinations of the following topical antibiotic ingredients in Category I: a. *Skin wound protectant.* (i) Bacitracin combined with polymyxin.

(ii) Any one tetracycline (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride) combined with polymyxin.

b. *Skin wound antibiotic.* (None listed.)

3. *Criteria for determining Category II combination products.* A combination is classified by the Panel as a Category II product if any one of the following apply:

a. A combination is Category II if a Category II antibiotic or nonantibiotic ingredient or labeling is present in the combination.

b. The combination contains antibiotics with identical or very similar antimicrobial spectrums.

c. The combination contains more than three antibiotic ingredients.

There were no combinations submitted to the Panel which meet the above criteria for Category II classification.

4. *Criteria for determining Category III combination products.* A combination product is classified as a Category III combination if any of the following apply: a. The Category III ingredient or labeling is present in a combination product containing no Category II ingredient or labeling, and

b. Except for skin wound protectants, the combination contains antibiotic ingredients which have different spectra, and which together significantly broaden the antimicrobial spectrum in a manner that is relevant to the intended claim.

5. *Combinations allowable as Category III.* Based on the above criteria and the combinations submitted and previously discussed in this document, the Panel places all combinations with any of the following ingredients in Category III: a. Skin wound protectant and skin wound antibiotic: (i) Combinations of neomycin, polymyxin, and bacitracin.

(ii) Bacitracin combined with neomycin.

b. Skin wound antibiotics only: (i) Bacitracin combined with polymyxin.

(ii) Any one tetracycline (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride) combined with polymyxin.

(iii) Gramicidin D combined with neomycin.

c. In addition, based upon significantly broadening the antimicrobial spectrum, the following combinations of active antibiotic ingredients, not now marketed, are considered by the Panel to be rational:

(i) Bacitracin combined with any one tetracycline (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride).

(ii) Polymyxin combined with gramicidin D.

(iii) Any one tetracycline (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride) combined with gramicidin D.

d. Further, the Panel agrees that should the criteria for combining topical antibiotic ingredients set forth above be met, all of these ingredients could be combined, if the total number of ingredients does not exceed three.

e. Further, there may be a number of other effective antibiotics for topical use which have been abandoned for systemic use because of potential toxicity which may, if investigated, add other combinations to this list.

f. Because a significant amount of data was submitted on the combinations set forth in paragraphs a and b of this section, the Panel believes these data should be revised in some detail as discussed below in section 6.

6. *Combinations of active ingredients.* a. *Neomycin-polymyxin-bacitracin.* Topical antibiotic products containing combinations of neomycin, bacitracin, and polymyxin have been used in the form of ointments, sprays, powders, and solution. In general, they are most widely used in the treatment of skin infections, burns, surgical wounds, and intravenous cutdown sites. Reports documenting use of these preparations began appearing in the mid-1950's and have continued to appear until the present time.

Antibiotic ointments containing neomycin sulfate 5 mg, zinc bacitracin 400 units, and polymyxin B 5,000 units per gm, have been used to treat various primary and secondary skin infections. In 1956 Panaccio (Ref. 1) used such treatment in 61 patients with various skin infections with results being good in 37, moderate in 14, and poor in 10. No cultures or controls were included in the report. Also in 1956 Stubenrauch et al. (Ref. 2) treated 113 cases of assorted skin infections with neomycin-polymyxin-bacitracin ointment with clearing of all lesions in 2 to 20 days. In 25 control cases treated with hydrocarbon base alone, only 4 cases cleared. However, control ointment base was not used in a double-blinded or randomized manner, and the 21 patients who did not immediately respond favorably to the ointment base alone were switched to neomycin-polymyxin-bacitracin ointment after 2 to 5

days. The Panel concludes that this was not an adequately controlled study. In 1959 Noojin et al. (Ref. 3) treated 55 patients with skin infections with neomycin-polymyxin-bacitracin ointment. Results were reported as good in 39 and poor in 16. No cultures or controls were included in the report.

In contrast to earlier uncontrolled or inadequately controlled studies, Pace in 1971 (Ref. 4) in an unpublished double-blinded, controlled study compared neomycin-polymyxin-bacitracin ointment and placebo ointment in the treatment of impetigo. In 30 patients, paired lesions of impetigo were graded according to size, redness, crust, oozing, and pain. Lesions were then culture and cleansed prior to treatment and were later recultured after 2, 3, and 7 days of treatment. One lesion of the pair on each patient was treated with the antibiotic ointment while the other lesion was treated with placebo ointment base. No significant difference was found between the two groups in either appearance of the lesions or in bacterial cultures. Inadequate antibiotic release from the ointment base was postulated by the author as a possible reason for the lack of superior results with the antibiotic ointment.

Four double-blinded, controlled studies between 1965 and 1970 document the use of neomycin-polymyxin-bacitracin ointment on intravenous catheter sites (Refs. 5 through 8). In each study antibiotic or placebo ointment was applied to puncture or cutdown sites after initial catheter insertion, and then reapplied once every 1 to 2 days after residual ointment had been removed. After catheter removal, the distal tip of each catheter was cut off and cultured. In 1965 Moran et al. (Ref. 5) applied antibiotic ointment to venous cutdown sites to see if phlebitis and septicemia resulting from infected intravenous catheters could be reduced. Application of antibiotic ointment to 38 cutdown sites was associated with bacterial colonization on only 18 percent of catheter tips, compared to 63 percent of catheter tips from 11 untreated sites, and 78 percent of catheter tips from 40 sites treated with placebo ointment. Septicemia (blood borne infection) did not develop in any patients treated with antibiotic ointment, in contrast to 2 cases in untreated controls and 5 cases in patients treated with placebo ointment. Phlebitis (localized inflamation of the vein) occurred in only 37 percent of patients treated with antibiotic ointment, in contrast to 57 percent of control patients. The authors concluded that neomycin - polymyxin - bacitracin ointment was helpful in preventing infections resulting from cutdown treatment. In 1970 Levy et al. (Ref. 6) reached the same conclusion in a similar study of cultures from 162 percutaneous venous catheters left in place longer than 48 hours. Results showed positive cultures from only 12 percent of 49 catheters treated with neomycin-polymyxin-bacitracin ointment, in contrast to 30 percent of 62 untreated catheters and 29 percent of 51 catheters treated with placebo ointment. The predominant organism cultured from all catheters was *Staphylococcus aureus*, but the number of organisms cultured was greatly decreased in the antibiotic ointment group. However, *Candida albicans* was cultured from 2 catheters in the antibiotic ointment group. Although this study was designed as a double-blinded, controlled trial, one of the investigators knew the code and allocated subjects, so that the experiment was actually unblinded at the beginning. Results showed a statistically nonsignificant difference in colonization, but in favor of the antibiotic ointment.

In 1969 Norden (Ref. 7) and Zinner et al. (Ref. 8) in separate studies concluded that antibiotic ointment does not decrease the overall incidence of bacterial colonization in catheter tips, but may offer protection against certain pathogenic organisms if catheters are left in place longer than 72 hours. Norden (Ref. 7) in a randomized, double-blinded, controlled study cultured 409 percutaneous catheter tips and found a bacterial colonization rate of 12 percent in 201 catheters from antibiotic-treated sites and 31 percent of 207 catheters from sites treated with placebo ointment. Pathogenic bacteria, however, were found in 4 percent of catheters in each group. If catheters were left in place longer than 4 days, pathogens were found on 8 percent of catheters, whereas if catheters were removed before being in place for 4 days, only 2 percent of catheters were infected. Zinner et al. (Ref. 8) cultured 436 percutaneous venous catheters in a double-blinded, controlled study. Catheter tips were found to be colonized with bacteria in 29 percent of 210 patients treated with antibiotic ointment and 34 percent of 226 patients treated with placebo ointment. Although there was no significant difference in the overall rate of colonization between the two groups, pathogens such as *Staphylococcus aureus* and gram-negative rods were greatly reduced on antibiotic-treated catheters, occurring in only 11 percent of antibiotic-treated catheters compared to 25 percent of controls treated with placebo ointment. *Candida albicans*, however, was found in 6 percent of antibiotic-treated catheters but in no placebo-treated catheters, and was felt to pose a potential danger of septicemia in antibiotic-treated patients. Approximately 30 percent of microorganisms cultured were resistant to the neomycin-polymyxin-bacitracin ointment. The development of phlebitis was not apparently influenced by the presence of antibiotic ointment, and also did not correlate with the presence of bacteria on the catheter tip. The incidence of phlebitis increased as catheters were left in place longer than 72 hours, so that early removal of venous catheters was concluded to be the most important factor in decreasing the risk of infection.

In 1962 Hildebrandt et al. (Ref. 9) lubricated urinary catheters with neomycin-polymyxin-bacitracin ointment in an effort to reduce urinary infection (bacteriuria) following catheterization in patients undergoing gynecologic surgery. Patients were catheterized in the operating room prior to surgery and the resulting urine was cultured. Postoperative urine cultures were taken 24 to 192 hours after surgery. Antibiotic ointment was applied only to catheters used in alternate patients, while control patients were left untreated. Antibiotic ointment significantly reduced the incidence of bacterial found in the urine, with only 6.7 percent of 15 patients with repeated short catheterizations having bacteriuria after topical antibiotic use compared to 36.4 percent in 22 controls. With prolonged indwelling catheterization, 100 percent of control patients but only 54 percent of antibiotic-treated cases had bacteriuria, although the number of cases was too small to be significant. It was concluded by the authors that antibiotic ointment helped reduce infection associated with single rapid catheterizations, but probably did not help prevent infection associated with prolonged indwelling catheters.

In 1972 and 1973 Bush and Stone (Refs. 10 and 11) reported the use of neomycin-polymyxin-bacitracin ointment and cream in treatment of major burns on burn wards to prevent infection with *Pseudomonas* organisms resistant to gentamicin. Following debridement and cleansing of burns, topical antibiotic cream or ointment was applied under absorbent pressure dressings, which were changed periodically under general anesthesia. From 1969 to 1971, among 204 children with extensive burns treated with neomycin-polymyxin-bacitracin cream or ointment, 2.0 percent died of pseudomonal sepsis. This was compared with earlier burn mortality rates of 1.9 percent among 623 children using topical gentamicin between 1964 and 1969, and 14.4 percent mortality among 791 children using topical nitrofurazone from 1958 to 1964. No control ointments were used during the treatment period with neomycin-polymyxin-bacitracin. The cream base was postulated to be more effective than the ointment base, possibly enabling better absorption of antibiotic into the burn wound. However, no attempt was made in the report to separate results using cream or ointment. Both cream and ointment forms were concluded to be effective in preventing and treating infections of burn wounds.

In 1962, Lowbury, et al. (Ref. 12) used antibiotic aerosol sprays containing neomycin-polymyxin-bacitracin to treat burns in 22 patients. Control patients received either no treatment (24 patients) or topical treatment with penicillin powder (24 patients). Results, based on daily bacterial cultures from burns, showed that bacterial growth was effectively suppressed in 47 percent of burns treated with antibiotic spray, compared to only 9 percent of untreated controls and 12 percent of patients treated with penicillin powder. The antibiotic spray suppressed staphylococci, coliforms, and *Pseudomonas*, which remained common in the other two groups. The antibiotic spray was concluded by the authors to significantly suppress bacterial infection in burns. No attempt was made to make

the study double-blinded or to treat burns with the aerosol spray alone.

In 1963 Lubowe (Re. 13) used antibiotic spray containing neomycin-polymycin-bacitracin to treat various primary and secondary skin infections in 51 patients. Results were reported as good in 42 and poor in 9 patients. No cultures or controls were included in the study in 1967 Mack and Cantrell (Ref. 14) in a very small double-blinded, controlled study evaluated the effectiveness of antibiotic sprays in reducing infections and healing time in superficial granulating wounds. Cultures of 20 infected wounds were taken prior to treatment and then 10 days after treatment had begun. Use of the antibiotic spray for 10 days resulted in 8 of 11 initially infected wounds having negative cultures, in contrast to 2 of 9 initially infected wounds having negative cultures following treatment with aerosol propellant alone. This difference was statistically significant and led the authors to conclude that the antibiotic spray was highly effective in eliminating bacterial infection from wounds. However, there was no statistically significant difference in wound healing times between the two groups.

In 1970 Purssey (Ref. 15) reported the treatment of 153 minor surgical wounds with neomycin - polymyxin - bacitracin spray following excision of skin lesions, but prior to suturing. An additional 127 similar wounds were not treated with the spray during the same period. All wounds were examined 7 to 10 days later at the time of suture removal, and cultures were taken of any wound which appeared to be infected. Results showed that 5.9 percent of wounds treated with the antibiotic spray were infected, in contrast to 17.3 percent of wounds which were infected in untreated controls. All infected wounds contained *Staphylococcus aureus*, and significantly more infected wounds occurred on the trunk and limbs than on the face and neck. The author concluded that the antibiotic spray dramatically decreased the number of postoperative infections in the treated group. Although this study was controlled, patients were not allocated in a randomized fashion and no attempt was made to double-blind the study by treating control wounds with a placebo spray.

In 1969 Heisterkamp et al. (Ref. 16) tested the effectiveness of neomycin-polymyxin-bacitracin spray in preventing inflection in war wounds of the extremities in Vietnamese soldiers. After wound cultures were taken, and within 1–6 hours after wounding, a single spray of antibiotic was applied to each wound. Wounds were then debrided at a later time during the initial 24 hours after wounds, and patients were monitored until their wounds were completely healed. Control patients received either no spray at all or treatment with oxytetracycline spray. Results showed that 39 percent of 28 control wounds which were not treated with any antibiotic spray developed infection. In contrast, 16.3 percent of 86 wounds treated with tetracycline spray became infected, as did 16.7 percent of 12 wounds treated with neomycin-polymyxin-bacitracin spray. The authors concluded that topical antibiotic sprays, if used early, can reduce the incidence of infection in war wounds, as the infection rate in the control group was 2½ times as great as in the group treated with topical antibiotics. However, the sample size of the group treated with neomycin-polymyxin-bacitracin spray (12 patients) is too small to permit conclusions of statistical significance.

In 1968 Matsumoto et al. (Ref. 17) studied simulated combat wounds which were produced in rabbits, comparing wound treatment using several types of topical antibiotic sprays. Antibiotic spray was applied 15 minutes after contaminated soil was rubbed into wounds initially produced with multiple deep incisions into the thigh muscles. Results showed that oxytetracycline in myristate spray was much superior to all other sprays used, including oxytetracycline in sesame oil spray and neomycin-polymyxin-bacitracin in either myristate or sesame oil sprays. Oxytetracycline in myristate spray reduced mortality to 3 percent, in contrast to a 78 percent mortality with neomycin-polymyxin-bacitracin in myristate spray.

Neomycin-polymyxin-bacitracin spray has been used extensively to treat major surgical wounds in an effort to prevent postoperative wound infections. In 1961 Forbes (Ref. 18) reported a survey of staphylococcal wound infections which developed over a 4-year period among 6,419 major operations. This was a before-and-after prospective cross-over study in which antibiotic spray was used for a period and then stopped, with incidence rates of wound infection computed for each period. During the 4-year period, the overall wound infection rate was 3.3 percent, but the yearly infection rates declined progressively from 6.7 percent in 1957 to 1.8 percent in 1960 as use of the antibiotic powder spray increased. The use of the antibiotic spray was encouraged, but not required during the study, and gradually increased throughout the treatment period. During a 2-month control period in 1960, the use of all antibiotic sprays was banned in the operating room, with the result that the infection rate rose to over 6 percent. When spraying of wounds with antibiotic was resumed, the monthly infection rates dropped sharply to levels of 0.1 to 2 percent, identical to levels in the previous 6 months. The overall infection rate in wounds treated with antibiotic spray was 2.0 percent, whereas the infection rate in unsprayed wounds was 4.3 percent. The author concluded that the antibiotic spray could both protect individual patients from wound infection and also help reduce the overall infection rate in surgical wounds. The Panel concluded that although there was a tendency towards reduction in infections during the periods in which antibiotic sprays were used, the differences in infection rates computed for each period were too small to be highly significant.

In 1965 Fielding et al. (Ref. 19) reported a controlled study performed over a 7-month period in which approximately half of all surgical wounds were treated with neomycin-polymyxin-bacitracin spray during wound closure. The spray was used only on certain days, which were allocated to different parts of the week as the study progressed in an effort to randomize patient selection. Control patients received no spray treatment. Results showed that among 480 clean wounds, infection occurred in 3.8 percent of untreated wounds and 0.9 percent of wounds treated with antibiotic spray, a difference in infection rates which is only slightly statistically significant. In 371 dirty or potentially infected wounds, infection occurred in 16.1 percent of untreated wounds and 12.8 percent of antibiotic-treated wounds, a difference which is not statistically significant. The authors concluded that prophylactic treatment of surgical wounds with topical antibiotic spray could not be recommended except in dirty wounds with a potentially high risk of wound infection. The Panel concluded that the study was performed in a rather loose and unsupervised manner, as suggested in the report, and that the positive results achieved in clean wounds should be interpreted with great caution.

In 1971 Jackson et al. (Ref. 20) concluded that neomycin-polymyxin-bacitracin spray will not prevent a majority of postoperative wound infections. Wounds to be treated with antibiotic spray were chosen randomly by spinning a coin. Among 704 operations, 340 wounds served as untreated controls. In the control groups, 14.3 percent of wounds became infected, whereas in the group treated with antibiotic spray, 10.9 percent of wounds became infected. Infection occurred in 5 percent of clean wounds, 11.5 percent of potentially contaminated wounds, and 42.1 percent of contaminated wounds. Although there was a slightly lower incidence of infection in the group sprayed with antibiotic, the difference in infection rates between the two groups was not statistically significant.

Four recent reports describe the use of neomycin-polymyxin-bacitracin spray in the management of contaminated surgical wounds following emergency abdominal surgery (Refs. 21 through 24). In 1972 Stone and Hester (Ref. 21) reported experience with neomycin-polymyxin-bacitracin spray in the management of wounds involving actual or possible gastrointestinal perforation following acute appendicitis or trauma to the abdomen. Wounds were randomly assigned to one of three treatment groups: immediate primary closure, delayed primary closure, and antibiotic spray followed by immediate primary closure. The outcome measure was the development of wound infection among 265 cases of abdominal incisions contaminated by bacteria. Results were difficult to interpret as percentages were given without denominators. Little difference was noted between delayed primary closure groups and antibiotic plus immedi-

ate primary closure groups, although both were much superior to primary closure alone. However, the addition of antibiotic spray significantly decreased the incidence of infection in wounds treated with immediate primary closure. Delayed closure without antibiotic spray also significantly reduced the infection rate in wounds, but wounds often became colonized later with different bacteria common in the hospital.

In 1973 Stone and Hester (Ref. 22) reported a similar study during a 27-month period in 1,288 children who underwent emergency surgery for treatment of penetrating abdominal wounds or possible intestinal perforation. Patients were randomly assigned to one of three treatment groups based on the last digit of their hospital number, and were subsequently treated with either immediate primary closure, delayed primary closure, or neomycin-polymyxin-bacitracin spray followed by immediate primary closure. Results were divided between clean and contaminated (dirty) wounds. Among clean wounds in 844 patients, results showed no significant difference between the three treatment groups. Among 444 contaminated wounds, however, immediate primary closure alone in 154 wounds resulted in 48.7 percent of wounds becoming infected, in contrast to 10.3 percent of 155 wounds which became infected using antibiotic spray prior to immediate primary closure and 15.6 percent of 135 wounds which became infected after delayed primary closure. The authors concluded that the topical antibiotic spray significantly decreased the incidence of wound infections in heavily contaminated abdominal incisions. Although this study was randomized and controlled, no effort was made to double-blind it using a control spray.

In 1973 Gilmore et al. (Ref. 23) reported a 5-month study in which appendectomy wounds were treated with neomycin - polymyxin - bacitracin spray powder in an effort to decrease the number of postoperative wound infections. Patients were randomly divided into three treatment groups of 84 each, receiving primary closure alone, antibiotic spray prior to primary closure, or povidone iodine spray prior to primary closure. Results showed a statistically significant reduction in the number of infections using both antibiotic spray and povidone iodine spray when compared to the use of no spray at all in wounds closed with primary closure. While 18 percent of control wounds became infected only 10 percent of antibiotic-treated wounds and 8 percent of povidone iodine-treated wounds were infected. The authors concluded that both the antibiotic spray powder and the povidone iodine spray were superior to primary closure alone for prevention of postoperative infection in appendectomy wounds.

An unpublished randomized and double-blinded controlled study by Seropian and Reynolds (Ref. 24) compared the use of neomycin-polymyxin-bacitracin spray to the spray aerosol alone in treating 256 emergency, high risk, contaminated major surgery cases. The antibiotic spray caused a significant reduction in wound infections with infection developing in 11.0 percent of 127 wounds treated with aerosol spray alone. No adverse reactions were observed using the sprays.

In 1972 Furman et al. (Ref. 25) reported the use of antibiotic solution containing neomycin-polymxin-bacitracin in treating five patients with infections developed around cardiac pacemakers. After the localized infections were cultured and debrided the wounds were irrigated every hour with antibiotic solution containing neomycin 1 gm; bacitracin, 50,000 units; and polymyxin, 500,000 units, per liter (1) of normal saline solution. In addition, patients were treated with oral antibiotics and kanamycin irrigation. Infections were cleared without removal of the pacemaker in all five patients, and the antibiotic solutions was felt by the authors to be extremely helpful in the treatment. However, there were so many treatment variables in the study that it is impossible to evaluate the role of the antibiotic in the overall treatment results.

In 1963 Lamphier and Goldberg (Ref. 26) reported the use of neomycin-polymyxin-bacitracin powder in lactose base to treat minor surgical wounds and skin infections in 356 patients. Following wound treatment with saline irrigation, soap cleansing, and debridement, the antibiotic powder was applied under a dressing. Most wounds were reported to have healed within 2 weeks, and the author concluded that the antibiotic powder was helpful in treating minor surgical wound infections. However, no controls were included in the study. In 1963 Gray and Kidd (Ref. 27) reported the use of neomycin-polymyxin-bacitracin powder in guinea pigs to treat experimental wounds which had been purposely infected. The powder was concluded by the authors to be very effective in preventing wound infections caused by aerobic bacteria. However, no attempt was made to double-blind the study by including treatment with powder base alone.

In summary, the Panel concludes that the studies cited above are insufficient to establish clinical effectiveness for the combination of neomycin, bacitracin, and polymyxin in topical antibiotic OTC products. Although several double-blinded, controlled studies have been performed using the triple antibiotic combination, they have mostly involved treatment of major surgical wounds or intravenous cutdown sites, instead of the prophylaxis or treatment of superficial skin infections for which OTC use is designed. An additional problem with many of these studies is their use of vehicles such as sprays and solution which are not presently available for OTC use, rather than the use of ointments which constitute the major formulated OTC product currently available. The Panel is concerned that the antibiotics may not be as readily released from the ointment dosage form as from sprays or solution, and therefore is not willing to accept studies with these bases as proof of effectiveness for the ointment dosage form. Most double-blinded, controlled studies involving the ointment dosage form of neomycin-polymyxin-bacitracin were concerned with attempting to prevent infection in intravenous catherization sites. Results of these studies are conflicting, with some authors concluding that the triple antibiotic ointment decreases the number of bacterial infections at the catherization sites, while other authors believe that the ointment does not decrease the overall incidence of infections at the catheter sites. The only double-blinded, controlled study with triple antibiotic ointment involving treatment of a superficial skin infection (Ref. 4) suggested that the antibiotic ointment was no more effective than the ointment base alone in the treatment of impetigo. Opposing this conclusion is a large body of favorable clinical impressions (cited above) based on uncontrolled clinical trials involving various superficial skin infections. While not wishing to disregard the clinical judgment of any practicing physician who contributed time and effort to both perform and report his studies, the Panel concludes that these studies cannot be substituted for double-blinded, controlled clinical trials in proving clinical effectiveness of the triple antibiotic ointment.

The Panel considers that the combination of neomycin, polymyxin, and bacitracin provides a rational and broad spectrum of antibacterial coverage against both gram-positive and gram-negative bacteria likely to be found in superficial skin wounds. The Panel concludes that if controlled studies show statistically that an ointment or any other topical dosage form containing the triple antibiotic combination is significantly more effective than the vehicle alone in preventing and treating infections in superficial skin wounds, neomycin-polymyxin-bacitracin should be reclassified as Category I as a skin wound antibiotic. This decision is contingent upon neomycin not being shown to be a significant allergic sensitizer in the population at large, as outlined earlier in this document. Category I status for this combination as a skin wound protectant would only be dependent on the resolution of the allergic sensitization question.

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b. *Bacitracin-neomycin.* Combination topical antibiotics containing bacitracin and neomycin have been used in the form of ointments, solutions, and sprays. Most reports documenting use of these products appeared between 1953 and 1966 (Refs. 1 through 8) and concerned treatment of pyodermas, burns, and massive soft tissue injuries as well as a mean of reducing the number of *Staphylococci* in the anterior nares of so-called nasal carriers. An additional report in 1971 concerned use of bacitracin-neomycin solution as a preoperative surgical scrub preparation (Ref. 9).

The use of bacitracin-neomycin ointment to treat skin infections was reported in 1953, 1954, 1963, and 1966 (Refs. 1 through 4). In 1953 Lubowe (Ref. 1) used bacitracin-neomycin ointment to treat 58 patients with various skin infections, with results reported as good in 53 and poor in 5 cases. No cultures or controls were included in the report. In the same study 22 patients with minor skin surgical wounds were treated prophylactically with bacitracin-neomycin ointment, with no infections developing in any wounds. In 1954 Greenhouse and Ryle (Ref. 2) treated 53 cases of assorted skin infections with bacitracin-neomycin ointment with good results in 47 and poor results in 6 cases. No cultures or controls were included in the report. In a double-blinded, controlled study in 1963 Burnett (Ref. 3) compared the effectiveness of systemically administered erythromycin with topically applied bacitracin-neomycin ointment in the treatment of impetigo. Impetigo lesions in 70 patients were cultured and gram-stained, and then treated with combinations of either erythromycin capsules and placebo ointment or placebo capsules and bacitracin-neomycin ointment. The average time interval between initiation of treatment and cure was not significantly different between the two groups, being 3.5 days with erythromycin capsules and 3.9 days with topical bacitracin-neomycin ointment. However, the number of treatment failures was significantly greater in the bacitracin-neomycin ointment group, with eight failures compared to one failure in the systemic erythromycin group. The systemic antibiotic was concluded to be much more reliable for treating impetigo than the topical antibiotic.

In 1966 Urbach (Ref. 4) treated 50 consecutive patients with assorted skin infections with topical antibiotic ointment containing either bacitracin-neomycin or neomycin-polymyxin-bacitracin. Cultures of all lesions before treatment revealed *Staphylococcus aureus*. Improvement of lesions was said to occur if their crusts disappeared, erosions healed, and itching vanished. Using these criteria, there was no significant difference between improvement of lesions in the two treatment groups as good results occurred in 20 of 25 cases in the neomycin-bacitracin group and 18 of 25 cases in the neomycin-polymyxin-bacitracin group. The addition of polymyxin to the antibiotic combination of bacitracin-neomycin was concluded by the author to yield no particular advantage, since most skin infections are due to staphylococci or streptococci which are not susceptible to polymyxin. No controls were included in this study.

In 1959 a double-blinded, controlled study by Weinstein (Ref. 5) examined the use of bacitracin-neomycin ointment for controlling the asymptomatic carriage of staphylococci in the noses of all personnel working on hospital surgical services. Over a 12-month period, 57 people were identified as persistent nasal carriers of staphylococci, as shown by frequent and repeated nose and throat cultures. The application of bacitracin-neomycin ointment to the anterior nares of the nose for a 7-day period was compared to either no treatment at all or treatment with placebo ointment. Good results, as judged by the presence of negative nose and throat cultures 1 week after treatment was discontinued, occurred in 72 percent of 39 people treated with bacitracin-neomycin ointment, 23 percent of 22 people treated with placebo ointment, and 22 percent of 37 people receiving no treatment. Bacitracin-neomycin ointment was concluded to be a useful topical treatment for partial control of staphylococcal nasal carrier states.

In 1960 Garnes et al. (Ref. 6) used sprays containing bacitracin and neomycin to treat patients with second and third degree burns. The spray left a powder which formed a thin film on the wound. No infections occurred among the 21 patients who were treated with bacitracin-neomycin spray, with burns remaining dry and odorless. However, four patients died of other complications. No cultures or controls were included in this report. In 1959 and 1960 bacitracin-neomycin sprays were also used to treat massive experimental wounds made with explosives in goats (Refs. 7 and 8), and were felt to be of significant benefit in prolonging survival time. The Panel concluded, however, that these types of studies were not relevant to evaluation of topical antibiotics for OTC use.

In 1971 Saik et al. (Ref. 9) used bacitracin-neomycin solution in 70 percent alcohol as a 5 to 10 minute presurgical scrub and compared it to an iodophor presurgical scrub solution. In 541 "clean" operations with obvious infection present, bacterial cultures were taken from the skin of the surgical site before the scrub solution was used, immediately prior to surgery and immediately after surgery. Prolonged bacterial suppression was found to occur on the skin treated with the bacitracin-neomycin solution, with significantly lower postoperative

median counts in the bacitracin-neomycin treated group than in the iodophor group. There were also more preoperative "no growth" bacterial counts after scrubbing with bacitracin-neomycin solution than with iodophor solution. Although fewer postoperative wound infections occurred following the bacitracin-neomycin scrub than with the iodophor scrub, the difference was not significant, with infections developing in 2.2 percent of the bacitracin-neomycin group and 3.6 percent of the iodophor group. The authors concluded that the bacitracin-neomycin scrub solution was more effective than iodophor solution in suppressing bacteria on the skin, even though there was no significant difference between the two groups in the number of postoperative wound infections which developed.

In summary, the Panel concludes that the studies cited above do not adequately establish clinical effectiveness for the combination of bacitracin and neomycin in topical skin wound antibiotic products. The only double-blinded, controlled study using bacitracin-neomycin ointment involved treatment of nasal carriers of staphylococci, not the prophylaxis or treatment of superficial skin infections for which OTC use of the combination is designed. The Panel considers that the combination of bacitracin and neomycin is rational since it broadens antibacterial coverage against the gram-positive organisms most likely to be found in superficial skin wounds, and also decreases the likelihood of encountering a bacterial strain resistant to both antibiotics as well as the chance of developing an infection which might be resistant to both antibiotics. Although the combination of bacitracin and neomycin does not provide bacterial coverage against some of the gram-negative bacteria, the Panel feels the potential risks for OTC use are low, since very few superficial skin wounds under normal circumstances become infected with gram-negative organisms. The Panel concludes that if controlled studies show statistically that an ointment or any other topical dosage form containing the combination of bacitracin and neomycin is significantly more effective than the vehicle base alone in preventing and treating infections in superficial skin wounds, bacitracin-neomycin should be reclassified as Category I as a skin wound antibiotic. This decision is contingent upon neomycin not being shown to be a significant allergic sensitizer in the population at large, as outlined earlier in this document. Category I status for this combination, as a skin wound protectant, would only be dependent on resolution of the allergic sensitization question.

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c. *Bacitracin-polymyxin.* The combination of bacitracin-polymyxin topical antibiotic was evaluated for treatment of various skin infections in five uncontrolled studies between 1952 and 1954 (Refs. 1 through 5). In 1954 Philip (Ref. 1) treated skin infections in 36 patients with a lotion containing 500 units of bacitracin and 10,000 units of polymyxin per ml of carbowax vehicle. Results were good in 19, moderate in 9, and poor in 8 cases. No controls were included in the study. In 1952 Gastineau and Florestano (Ref. 2) used bacitracin-polymyxin ointment to treat 147 patients with assorted skin infections. Results were reported as good in 137, moderate in 9, and poor in 3 cases. No controls were included in the report. In 1952 Graves (Ref. 3) reported the use of bacitracin-polymyxin ointment in 89 cases of acute and chronic external ear infections. Good results were seen in all cases. No cultures or controls were included in the study.

In 1953 Kile et al. (Ref. 4) used an ointment containing bacitracin 500 units and polymyxin B 10,000 units per gm to treat 361 patients with various skin infections. Results were good in 87, moderate in 230, and poor in 44 cases. Although cultures were performed in 78 patients, no controls were included in the study. The same ointment was used prophylactically in 65 patients following various office minor surgical procedures, with prevention of infection in all cases (Ref. 4). No controls were included in the prophylactic study. In 1954 Pass and Rattner (Ref. 5) used bacitracin-polymyxin ointment to treat 577 cases of skin infection. Results were good in all cases, but no controls were included in the report. In the same study, no postoperative infections occurred in 34 cases of acne planning following prophylatic use of the ointment (Ref. 5).

In summary, the Panel concludes that the uncontrolled studies cited above do not adequately establish clinical effectiveness for the combination of bacitracin and polymyxin in topical skin wound antibiotic products. The Panel considers that the combination of bacitracin and polymyxin is rational and provides a broad spectrum of antibacterial coverage against both gram-positive and gram-negative bacteria likely to be found in superficial skin wounds. The Panel concludes that if controlled studies show statistically that an ointment, lotion, or any other topical dosage form containing the combination of bacitracin and polymyxin is significantly more effective than the vehicle alone in preventing and treating infections in superficial skin wounds, bacitracin-polymyxin should be reclassified as Category I as a skin wound antibiotic. This combination is already classified as Category I as a skin wound protectant.

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d. *Tetracycline-polymyxin.* Clinical use of topical antibiotics containing the combination of tetracycline and polymyxin has not been widely reported, with only three reports documenting the use of tetracycline-polmyxin ointment (Refs. 1, 2, and 3) and three additional reports documenting the use of tetracycline-polymyxin powder. No controlled studies have been reported using this combination.

In 1953 and 1955 Appel (Refs. 1 and 2) reported the use of oxytetracycline-polymyxin B ointment in 2 studies which included 137 and 433 patients with assorted skin infections. Among the 137 patients, results were reported as good in 82, moderate in 26, and poor in 29. Among 433 patients, results were good in 392 and poor in 41. No cultures or controls were included in either study. Appel (Ref. 1) also reported that 56 minor surgical wounds treated prophylactically with the same ointment healed without evidence of infection. Again, no controls were included. In 1955 Carsley (Ref. 3) treated 75 patients with various skin infections using oxytetracycline-polymyxin ointment. Results were good in 54, moderate in 13, and poor in 8 cases. Acute impetigo in 20 patients was cured in 2 to 7 days. No cultures or controls were included in the report.

In 1959 and 1962 Barefoot (Refs. 4 and 5) used oxytetracycline-polymyxin

powder to treat 5,691 and 5,500 patients with assorted skin infections and postoperative minor surgical wounds. Good results were reported in all patients, but no cultures or controls were included. In 1965 Lamphier (Ref.6) used oxytetracycline-polymyxin B power to treat 1,112 patients with assorted localized skin infections or postoperative abdominal wounds. Results were reported as good in 987, moderate in 98, and poor in 27. No cultures or controls were included in the report.

In summary, the Panel concludes that the uncontrolled studies cited above do not adequately establish clinical effectiveness for the combination of tetracycline and polymyxin in topical skin wound antibiotic products. The Panel considers that the combination of tetracycline and polymyxin provides a rational and broad spectrum of antibacterial coverage against both gram-positive and gram-negative bacteria likely to be found in superficial skin wounds. The Panel concludes that if controlled studies show statistically that an ointment, powder, or any other topical dosage form of the combination of tetracycline and polymyxin is significantly more effective than the vehicle alone in preventing and treating infections in superficial skin wounds, tetracycline-polymyxin should be reclassified as Category I as a skin wound antibiotic.

REFERENCES

(1) Appel, B., "Oxytetracycline-Polymyxin B Ointment in Skin Infections," *Antibiotics and Chemotherapy*, 3:1258–1267, 1953.

(2) Appel, B., "Oxytetracycline and Polymyxin B. Their Combined Effect on Pyodermatises," *Antibiotics Annual*, 2:949–958, 1954–55.

(3) Carsley, S. H., "An Evaluation of Oxytetracycline Combined with Polymyxin B for Topical Use," *Antibiotic Medicine*, 1:567–569, 1955.

(4) Barefoot, S. W., "Oxytetracycline Hydrochloride-Polymyxin B Sulfate Topical Powder," *Archives of Dermatology*, 79:455–457, 1959.

(5) Barefoot, S. W., "Topical Oxytetracycline-Polymyxin Further Observations," *Dermatology*, 86:236, 1962.

(6) Lamphier, T. A., "Surgical Infections Treated with Oxytetracycline," *Clinical Medicine*, 72:88–92, 1965.

e. *Gramicidin-neomycin.* Gramicidin D, 0.25 mg/gm in plasticized hydrocarbon gel base, was submitted for OTC review as part of a combination ointment containing neomycin. The Panel considers that the combination of gramicidin D and neomycin is rational since it broadens antibacterial coverage against the gram-positive organisms most likely to be found in superficial skin wounds, and also decreases the likelihood of encountering a bacterial strain resistant to both antibiotics as well as the chance of developing an infection that might be resistant to both antibiotics. Although the combination of gramicidin D and neomycin does not provide adequate bacterial coverage against gram-negative bacteria, the Panel is not concerned about potential risks for OTC use since very few superficial skin wounds under normal circumstances become infected with gram-negative organisms. No clinical studies involving the use of the combination of gramicidin D-neomycin, either controlled or uncontrolled, were submitted to the Panel for evaluation. Therefore, the Panel was unable to evaluate the clinical effectiveness of this topical antibiotic combination. The Panel concludes that if controlled studies show statistically that an ointment, or any other topical dosage form containing the combination of gramicidin D and neomycin, is significantly more effective than the vehicle alone in preventing and treating infections in superficial skin wounds, gramicidin D-neomycin should be reclassified as Category I. The decision is contingent upon neomycin not being shown to be a significant sensitizer in the population at large, as outlined earlier in this document.

C. CONCLUSIONS REGARDING COMBINATIONS

A comprehensive search of the literature recently published "reveals no direct evidence from double-blind controlled studies that the application of combinations of antibiotics will reduce the number of infections of accidentally incurred minor cuts, burns and abrasions" (Ref. 1). It is argued that in vitro studies, in vivo evidence, and the positive findings in other clinical trials (as, for example, surgical wounds) should lead to the conclusion that these agents will also be effective in the prophylaxis of infections of accidentally incurred cuts and abrasions.

The Panel is unable to accept this argument for several reasons. The evidence from the referenced clinical trials is not always consistent. Furthermore, the design of many of the cited studies is deemed less than adequate. Finally, although other studies may suggest that a properly designed, randomized, double-blinded, controlled trial of combination antibiotic agents might reduce the incidence of infection of accidentally incurred minor cuts, wounds, and abrasions, the proof is still lacking. However prudent scientific judgment does not permit the conclusion that merely arguing their efficacy by analogy is sufficient.

REFERENCE

(1) Anderson, V., "Over-the-Counter Topical Antibiotic Products: Data on Safety and Efficacy," *Supplement to International Journal of Dermatology*, 15:1–118, 1976.

D. CRITERIA FOR RECLASSIFICATION OF CATEGORY III COMBINATIONS TO CATEGORY I COMBINATIONS.

1. *Safety.* The combination must be shown to be safe utilizing the tests described in the Guidelines for Evaluation of Safety described elsewhere in this document. (See part VI. paragraph B.1. below—Safety testing.)

2. *Effectiveness.* The combination must be shown to be effective utilizing the tests in Guidelines for Evaluation of Clinical Effectiveness described elsewhere in this document. (See part VI. paragraph B.2. below—Effectiveness testing.)

VI. GENERAL GUIDELINES FOR SAFETY AND EFFECTIVENESS EVALUATION OF TOPICAL ANTIBIOTICS

A. INTRODUCTION

The Panel believes it reasonable to allow 2 years for the development and review of evidence to permit final classification of these ingredients and the claims made for them. Marketing need not cease during this time if adequate testing is undertaken.

The Panel has given considerable thought to the problem of how to demonstrate the safety and effectiveness of topical antibiotics. The following guidelines for demonstration of product safety and effectiveness were developed by the Panel to aid evaluation of present data and assist manufacturers in designing future studies. The guidelines are not meant to be rigid or binding protocols for evaluation of safety or effectiveness, but instead attempt to indicate the type of information judged by the Panel to be essential for conclusive evaluation of drugs designed for widespread OTC use.

B. SAFETY AND EFFECTIVENESS TESTING

1. *Safety testing, using both topical and systemic methods of exposure to the antibiotic.* The Panel believes that safety testing of OTC topical antibiotic ingredients must include application to large areas of damaged skin. Despite the intended restriction of their use to small cuts and abrasions, these formulations have a history of use on larger areas of damaged skin such as diaper rash, heat rash, leg ulcers, and extensive burns. The Panel feels that manufacturers should realize that topical OTC antibiotics are used in an unsupervised manner and that safety testing should make every effort to assure minimal risk of toxicity to the patient despite the manner of application to the skin.

The tests described below should be performed in an appropriate animal species when required in the appropriate section(s) for each specific ingredient described elsewhere in this document.

a. *Topical.* Determine for both the antibiotic and the final formulation where applicable:

(1) Primary skin irritation following single or repeated exposure. Special attention should be paid to the eyes and mucous membranes (Ref. 1).

(2) Allergic contact dermatitis. Any unusual adverse reactions in humans, such as photosensitivity or alterations in pigmentation, should be carefully and fully investigated.

(3) Effect of the antibiotic and formulation on wound healing.

REFERENCE

(1) Rovee, D., Transcripts of open session of Antimicrobial II Panel, March 21, 1975.

b. *Systemic.* For the antibiotic alone, determine the following: (1) Develop, if possible, an adequately sensitive analytical method such that traces in blood can be determined.

(2) Determine, if possible, an LD_{50} in animals by at least two routes of administration, one being either parenteral

or oral. In determining an LD_{50}, the minimum lethal and the maximum tolerated blood level and dose by that route should be established.

(3) The target organ(s) for toxicity effects should be identified if possible when the drug is administered topically and via oral or parenteral routes in animals. Specific toxic effects in each species should be related to a blood concentration and the time required to induce that effect. It is also expected that these toxicity studies should be conducted in a single species during a single study. Appropriate histological and biochemical studies relating to observed effects should be conducted.

(4) Degree of absorption (at least as evidenced by blood tests) through both intact and abraded animal skin, using at least 25 percent of the total body surface as the size of the test area. Both acute and subacute exposures should be evaluated. Tissue distribution studies following both topical application and oral or parenteral administration (if evidence suggests differences), metabolic fate, and rates and route of excretion should be determined if target organs have been found for toxicity.

c. Where evidence suggests a need, conduct appropriate teratogenicity, mutagenicity, carcinogenicity, and reproduction studies in animals.

2. *Effectiveness testing, including in vitro tests and in vivo tests with animal models, human models, and clinical studies.* The Panel feels that evaluation of clinical effectiveness of topical antibiotics should include recognition and consideration of their widespread OTC use for treatment as well as prevention of skin infection. Although topical antibiotics are presently labeled only for prophylactic use to prevent infection in small cuts and wounds, the Panel suspects that consumers use these products more frequently to treat rather than to prevent such infections. While not encouraging self-diagnosis and treatment of infection, the Panel believes that the average consumer can reliably recognize the signs of skin infection (redness, warmth, tenderness, pus) and should have the option of applying a safe and effective OTC medication. Therefore, the Panel is willing to accept a realistic therapeutic labeling claim for effectiveness in treatment of minor skin wound infections, providing justification for such a claim can be clearly and convincingly demonstrated for topical antibiotics by the manufacturer.

Demonstration of clinical effectiveness must include proof that the formulated topical antibiotic product is more effective than the product vehicle alone. Controlled studies are required by the Panel to demonstrate that the antibiotic product is more than an inert vehicle inducing a beneficial placebo effect on the skin. The Panel requires evidence that each antibiotic is successfully released from its vehicle when applied to skin, thereby becoming available to act on bacteria within superficial skin wounds.

The Panel concludes that three major areas of effectiveness must be evaluated: Prophylaxis or prevention of infection; effectiveness in the treatment of infection, if claimed; and the effects on wound management and wound repair. The Panel recognizes the many difficulties inherent in obtaining acceptable data in all of these areas. Therefore, the Panel recommends preliminary well-designed and well-controlled animal and human model studies, followed by appropriate clinical trials. Such models should simulate as closely as possible situations that might exist in actual practice. The panel will not insist on clinical testing of prophylactic effectiveness in a large number of patients, provided that adequate model studies have been conducted to indicate prophylactic effectiveness.

The following guidelines for effectiveness testing are not intended to be restrictive, but merely indicate the types of data considered necessary:

a. *In vitro testing.* Such testing should include: (1) Careful technique to ensure that antibiotic carryover into the test system is eliminated by proper dilution or inactivation.

(2) Determination of the antimicrobial spectrum of the antibiotic using both standard cultures and recently isolated strains of each species.

(3) Determination of the minimal inhibitory concentration (MIC) of the antibiotic under standard conditions against standard reference organisms and recent clinical isolates from superficial infections to provide updated, relevant data on susceptibility of these current isolates.

b. *In vivo testing.* Such testing should be designed to closely approximate clinical situations and evaluate intended label claims for both prevention and treatment of minor skin wound infections and management of wounds. A well-designed study should include proper precautions to demonstrate the effect of the antibiotic itself compared with the effect of the vehicle. Control groups should receive treatment with inert vehicles which are identical in appearance, odor, and consistency to the test material. A doubleblinded procedure should be employed to minimize bias in reporting results. An appropriate procedure to ensure random allocation of subjects to treatment and comparison groups should be employed (Ref. 1).

In vivo testing could include work with animal models and human models, prior to clinical studies.

The Panel recognizes the difficulty in conducting large-scale prospective clinical trials. Several statistical methods to reduce the size of these trials may be helpful, such as use of sequential designs to limit the sample size.

(1) *Animal models.* Review of the current literature suggests that hamsters and guinea pigs are satisfactory experimental animals in which to consistently produce skin infection. The impetigo model in hamsters and the various guinea pig surgical wound models appear to provide reliable test systems for evaluating both therapeutic and prophylactic effectiveness of topical antibiotics. Care must be taken, however, in comparing test results obtained in different species.

The Panel recommends that attempts be made to standardize the following variables in animal models: (1) Location of contaminated wounds.

(ii) Depth of incision.

(iii) Type and quantity of inoculum.

(iv) Method of inoculation.

(v) Time between the inoculation and treatment.

(vi) Method of culturing.

(vii) Technique of treatment.

(viii) Method of wound closure.

(ix) System of grading infections.

In working with prophylactic surgical wound models, effort should also be made to avoid leaving necrotic tissue, foreign bodies, dead space, or hematomas which might interfere with wound healing.

(2) *Human models for treatment and prophylaxis.* Review of the current literature and of unpublished data presented to the Panel leads the Panel to believe that a few satisfactory and safe model systems presently exist for producing experimental superficial infection in human skin. Successful models require disruption of the uppermost layers of the skin through either cellophane tape stripping or ammonium hydroxide blister formation. To ensure safety, a 24-hour lag period must elapse between stripping or blister induction and inoculation of pathogenic microorganisms into the wound, which is then followed by plastic wrap occlusion. The resulting skin lesions, induced by *Staphylococcus aureus*, apparently resemble superficial infections produced under natural conditions and may be used to evaluate possible therapeutic effectiveness of topical antibiotics.

Prophylactic effectiveness can also be evaluated using the same model by inserting a topical antibiotic into the test system between the time of bacterial inoculation and usual appearance of clinical lesions.

A second model for testing prophylactic effectiveness includes the use of plastip wrap occlusion on normal forearm skin to induce bacterial proliferation. Application of various concentrations of antibiotic before, during, or after occlusion helps indicate the bacteriostatic and bactericidal effectiveness of a test product against both gram-positive and gram-negative microorganisms.

The Panel recognizes that no single test system can possibly encompass all therapeutic and prophylactic applications for which OTC topical antibiotics are designed. Separate protocols will have to be designed to consider such variables as antibacterial spectrum and duration of antibiotic action. The Panel concludes, however, that existing model test systems in humans can be modified and controlled in such a way that they will help to evaluate specific claims for therapeutic and prophylactic effectiveness of topical antibiotics.

(3) *Clinical studies.* The final appraisal of topical antibiotic effectiveness must take place in a clinical setting under circumstances conforming to actual circumstances in the community and must conform to accepted ethical standards. Animal and human models may

lessen the need for extensive, time-consuming, expensive clinical trials on agents that are found to be ineffective in the model system. The Panel expects that, at a minimum, adequate clinical studies would be conducted to confirm and validate the results of model studies if performed. For example, a small closed population could probably be found in which the infection rate of small wounds could be determined. With adequate controls and experimental design, it could then be demonstrated that application of a topical antibiotic did or did not alter the normal infection rate.

A variety of strategies are available to limit the number of subjects in these clinical studies, including sequential designs and use of artificially induced wounds in volunteers. It is suggested that prophylactic trials not be initiated unless there is sufficient evidence to suggest that they will show a beneficial effect for the tested products.

REFERENCE

(1) Hill, A. B., "Principles of Medical Statistics," 9th Ed., Oxford University Press, New York, 1971.

C. SUMMARY.

The Panel has given careful consideration to the types of studies and types of data to be required for reclassifying a claimed active topical antibiotic ingredient from Category III and placing it in Category I. Effectiveness should be demonstrated by means of randomized controlled clinical trials. In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blinded, controlled prospective study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of the general population as well as diet, activity, travel, etc. of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredient should be made. The features of a well-designed clinical trial are outlined in § 314.111 (21 CFR 314.111). The Panel believes that a single study of adequate size and design may provide sufficient evidence to make a judgment as to effectiveness. To demonstrate safety, appropriate toxicological studies in appropriate experimental animals and man are required, as outlined elsewhere in this document.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1953 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S. 321, 352, 355, 371)) and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)) and under authority delegated to him (21 CFR 5.1), the Commissioner proposes that Subchapter D be amended by adding new Part 342 to read as follows:

PART 342—TOPICAL ANTIBIOTICS FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.
342.1 Scope.
342.3 Definitions.

Subpart B—Active Ingredients

342.10 Skin wound protectant.
342.40 Permitted combinations of skin wound protectant active ingredients.

Subpart C—[Reserved]

Subpart D—Labeling

342.50 Labeling of skin wound protectant products.
342.52 Labeling of skin wound antibiotic products.

AUTHORITY: Secs. 201, 502, 505, 701, 52 Stat. 1040–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321, 352, 355, 371); (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 342.1 Scope.

An over-the-counter antibiotic product in a form suitable for topical use is generally recognized as safe and effective and is not misbranded if it meets each of the following conditions and each of the general conditions established in § 330.1 of this chapter.

§ 342.3 Definitions.

For topical preparations when applied at acceptable concentrations, as used in this part:

(a) Skin wound protectant. A safe, nonirritating preparation applied to small, cleansed wounds that provides a protective physical barrier, conforming to the barrier testing for skin wound protectants as published in the FEDERAL REGISTER of September 13, 1974 (39 FR 33140), and may also include a chemical (antibiotic), which neither delays healing nor favors the growth of microorganisms.

(b) Skin wound antibiotic. A safe, nonirritating antibiotic-containing preparation that prevents or treats overt skin infection.

Subpart B—Active Ingredients

§ 342.10 Skin wound protectant.

The active ingredients of the product consist of the following within any maximum dosage limit established:

(a) Bacitracin. Adults and children topical ointment dosage is not less than 500 units of bacitracin per gm of finished ointment dosage form as identified in § 448.510a of this chapter (a unit of potency contained in 13.51 mcg of the bacitracin master standard as identified in § 430.6(a)(2) of this chapter).

(b) *Polymyxin B sulfate.* Adults and children topical ointment dosage is 4,000 to 5,000 units polymyxin B per gm of finished ointment dosage form when used in combination only as identified in § 342.30 (a), (b), (c), and (d) of the bulk antibiotic, the potency of which is not less than 6,000 units of polymyxin B per mg of polymyxin B sulfate as identified in § 448.30(a)(1) of this chapter.

(c) *Tetracycline preparations (chlortetracycline hydrochloride, oxytetracycline hydrochloride, tetracycline hydrochloride)*—(1) *Chlortetracycline hydrochloride.* Adults and children topical ointment dosage is not less than 1 mg of chlortetracycline hydrochloride per gm of the finished ointment dosage form as identified in § 446.510a of this chapter.

(2) *Oxytetracycline hydrochloride.* Adult and children topical ointment dosage is not less than 30 mg oxytetracycline hydrochloride per gm of the finished ointment dosage form as identified in § 446.567b of this chapter.

(3) *Tetracycline hydrochloride.* Adults and children topical ointment dosage is not less than 15 mg tetracycline hydrochloride per gm of the finished ointment dosage form as identified in § 446.581a of this chapter.

§ 342.30 Permitted combinations of skin wound protectant active ingredients.

(a) Polymyxin B sulfate identified in § 342.10(b) may be combined with bacitracin identified in § 342.10(a): *Provided,* That the combination meets the requirement of § 448.510c of this chapter.

(b) Polymyxin B sulfate identified in § 342.10(b) may be combined with chlortetracycline hydrochloride identified in § 342.10(c)(1): *Provided,* That a suitable requirement for certification is established for the combination in § 446.510 of this chapter.

(c) Polymyxin B sulfate identified in § 342.10(b) may be combined with oxytetracycline hydrochloride identified in § 342.10(c)(2): *Provided,* That the combination meets the requirement of § 446.567b of this chapter.

(d) Polymyxin B sulfate identified in § 342.10(b) may be combined with tetracycline hydrochloride identified in § 342.10(c)(3): *Provided,* That a suitable requirement for certification is established for the combination in § 446.581 of this chapter.

Subpart C—[Reserved]

Subpart D—Labeling

§ 342.50 Labeling of skin wound protectant products.

(a) Indications. The labeling of the product may contain any phrase(s) in the definition of a skin wound protectant established in § 342.3(a). Labeling may also include the phrase(s): "Protectant", "protects wounds", "first-aid product", "first-aid for small (minor) cuts, abrasions and burns", "protectant for small (minor) cuts, abrasions and burns", "protects against wound contamination".

(b) Warnings. The labeling of the product contains the following warnings under the heading "Warning", which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable:

(1) "Caution: In case of deep or puncture wounds or serious burns see a physician".

(2) "Do not use longer than 1 week".

(3) "If itching, redness, swelling or pain develops or increases, it may be a sign of infection or allergy. Stop use and see a physician".

(4) "Do not use in the eyes".

(5) "Do not use on long-standing skin conditions such as leg ulcers, diaper rash or hand eczema".

(c) Directions for use. The labeling of the product contains the statement: "After gentle washing, apply a small amount (an amount equal to the surface area of the tip of a finger) directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily".

§ 342.52 **Labeling of skin wound antibiotic products.**

(a) Indications. The labeling of the product may contain any phrase(s) in the definition of a skin wound antibiotic established in § 342.3(b). Labeling may also include the phrase(s): "Decreases bacteria", "helps prevent or guard against skin infection", "helps reduce the risk (and/or chance) of infection", "helps reduce the number of bacteria on the treated area", "helps protect wounds against infection", "first-aid product", "broad spectrum (if applicable)", "treats infection", "antibiotic medication for skin wounds". In addition, any phrase in the definition of a skin wound protectant may be used.

(b) Warnings. The labeling of the product contains the following warnings under the heading "Warning", which may be combined to eliminate duplicative words or phrases so the resulting warning is clear and understandable:

(1) "Caution: In case of deep or puncture wounds or serious burns see a physician".

(2) "Do not use longer than 1 week".

(3) "If swelling or pain increases, or if itching and redness develop, stop use and see a physician".

(4) "Do not use in the eyes".

(5) "Do not use on long-standing skin conditions such as leg ulcers, diaper rash or hand eczema".

(c) Directions for use. The labeling of the product contains the statement: "After gentle washing, apply a small amount (an amount equal to the surface area of the tip of a finger) directly to the affected area and cover with sterile gauze if desired. May be applied 1 to 3 times daily".

Interested persons are invited to submit their comments in writing (preferably in quintuplicate and identified with the Hearing Clerk document number found in brackets in the heading of this document) regarding this proposal on or before June 30, 1977. Such comments should be addressed to the Office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a memorandum or brief in support thereof. Additional comments replying to any comments so filed may also be submitted on or before August 1, 1977. Received comments may be seen in the above office during working hours, Monday through Friday.

NOTE.—The Food and Drug Administration has determined that this document does not contain a major proposal requiring preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A–107. A copy of the inflation impact assessment is on file with the Housing Clerk, Food and Drug Administration.

Dated: March 22, 1977.

SHERWIN GARDNER,
Acting Commissioner of Food and Drugs.

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