The Food and Drug Administration's Certification of Antibiotic Drugs for Human Use

B. Harvey Minchew, M.D.*

In September, 1943, the War Production Board, with the concurrence of the military authorities, developed a program for control of penicillin distribution whereby the Food and Drug Administration assayed samples from each batch before they were released for use. The reasons for these special controls at that time were:

1. Penicillin is produced by a biologic process and is therefore subject to the inherent vagaries of such processes.

2. The scope of therapeutic effectiveness of penicillin and its relative freedom from toxicity when properly purified and standardized gives it an importance not then approached by any other drug.

With relaxation of wartime controls in 1945, continuation of premarketing testing of penicillin required the enactment of specific legislation by Congress. For this purpose, Congress, in 1945, passed an amendment, Section 507, to the Federal Food, Drug, and Cosmetic Act, which continued the predistribution testing of penicillin by FDA.

In 1947, Congress amended Section 507 to require certification by premarketing testing of streptomycin and its derivatives.

Until 1962, these five antibiotics (penicillin, streptomycin, chlorotetracycline, chloramphenicol, bacitracin, and their derivatives) were the only antibiotics which FDA certified by premarketing testing on a batch-by-batch basis.

Section 507 specified that a batch of any such drug shall be certified if the drug has such characteristics of identity, strength, quality, and purity as prescribed in the appropriate regulations to adequately insure the safety and efficacy of use. Therefore, the certification of these five antibiotic drugs was predicted upon the demonstration that the drugs were both safe and effective for use as prescribed in the labeling, and that each batch was tested for conformity to a prescribed set of standards for its characteristics of identity, strength, quality, and purity. The showing of both safety and effectiveness in clinical trials prior to marketing for these drugs is noteworthy for until the Kefauver-Harris Amendments of 1962, no other drugs — except insulin — were required by the law to have demonstrated efficacy prior to marketing. However, because of the inherent necessity for most antimicrobials to be effective in order to be safe, the manufacturers very frequently established to their own satisfaction the effectiveness of such products in treating appropriate infectious diseases.

With passage of the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act, all antibiotic drugs for human use became subject to the certification requirements of Section 507 of the Act. Furthermore, the Act now defines an antibiotic drug as any chemical substance produced by living micro-organisms which in dilute solution will inhibit or destroy other micro-organisms. Thus, certain drugs which are used as antimicrobials in the treatment of infectious diseases are not subject to certification. Examples of these are isoniazid, the sulfa drugs, furantoin, and nalidixic acid.

However, other drugs produced by fermentation, namely certain antineoplastic agents such as the actinomycins, which are not used in the therapy of infectious diseases are legally antibiotics and are subject to certification. Furthermore, if an antibiotic drug per se can be completely or partially synthesized it remains subject to certification, examples being chloramphenicol and the semi-synthetic penicillins.

Therefore, FDA is now certifying annually thousands of batches of dosage forms produced from approximately 36 different antibiotic drugs.

Also, the law has made provisions for exempting certain antibiotic products from certification, and regulations have been promulgated which implement this provision. Basically, the law stipulates that to be considered for exemption from certification a manufacturer must have produced 50 consecutive batches of the particular antibiotic in 18 months, none of which has been rejected. At this time very few products have been exempted and recent regulations on this matter restrict those products which are eligible for exemption to agents used locally. Furthermore, antibiotic products are not subject to certification during investigational studies. It is at the time of commercial marketing that the certification requirements are first applied.

It should also be noted that while prior to 1962 there were only five antibiotic drugs which were legally required to establish efficacy before marketing; now all antibiotics must prove efficacy before marketing. So too must all other new drugs establish efficacy as well as safety before commercial distribution. However, the batch-by-batch testing required in the antibiotic certification procedure has no analogy for non-antibiotic new drugs. The only other products which are certified on a batch basis are insulin and colors not exempt from this requirement.

The handling of the certification of antibiotics is done by our Division of Antibiotics and Insulin Certification in the Bureau of Science. This Division is composed of approximately 150 persons, most of whom are chemists and bacteriologists. Their day-to-day work involves the laboratory procedures of testing for potency, pyrogens, safety, presence of histamine-like substances, moisture, pH, sterility, stability, etc., all of which serve to establish the conformity of each batch of each antibiotic to the prescribed standards of identity, strength, quality, and purity. When the testing of a batch has been completed, which normally requires only a few days, and all the standards are adequately met, the manufacturer is issued a "certificate" for that batch. It is only at that time that the batch may be released from the warehouse for commercial distribution.

In order to give you some estimate of the size of this operation, the figures for a recent fiscal year are illustrative. We received samples from 22,167 batches of antibiotic preparations. Of these, 241 were found unsatisfactory because of failure to meet one or more of the specifications for that antibiotic drug. Of the 241 batches not certified, 82 failed to meet the requirements for potency; 16 failed to meet the requirements for sterility; 8 failed to meet the requirements for moisture; 75 were cross-contaminated with penicillin; 31 were produced under objectionable manufacturing practices; and the remaining 29 were rejected for miscellaneous reasons such as failure to meet the requirements for pH, tablet disintegration time, etc.

While for this particular year this represents a rejection rate of only about 1 per cent, it should be noted that more than 90 per cent of these batches were tested by the original manufacturer and found acceptable before being submitted to us for certification. Furthermore, while the rejection rate of 1 per cent of the batches seems small, it represents millions of individual doses of the drugs.

In closing, let me concisely illustrate our handling of an antibiotic product for human use. At the time a new antibiotic enters investigational use in humans, the sponsor must submit an investigational drug exemption to us. This IND is handled in a fashion similar to INDs for non-antibiotics. During Phase III studies, the manufacturer in collaboration with our Division of Antibiotics and Insulin Certification will establish a monograph of standards for the identity, strength, quality, and purity of that antibiotic. Mutually agreed upon methods and tests for determining these values are described. The product is...
not certified during the investigational trials. When the sponsor has accumulated sufficient data which he believes serves as substantial evidence of the safety and effectiveness of the product, he submits an application for certification. Throughout the investigational phases of a drug’s development and at the time of our evaluation of the application for certification, the scientific data submitted are reviewed by three different groups within FDA. The manufacturing controls, laboratory controls, and standards are evaluated by the chemists in our Division of Anti-infective Drugs. The toxicologic and pharmacologic animal studies are reviewed by our toxicologists-pharmacologists. The data on human use, both pre-clinical and clinical, are evaluated by the medical officers in our Bureau of Medicine; they have the responsibility of coordinating these reviews and making a final recommendation of the adequacy of the data in supporting the labeling claims. If it is our conclusion that the available data do provide substantial evidence that the product is safe and effective as labeled, the monograph is published in the Federal Register and batches may be submitted for certification.

RESIDENT FELLOWSHIP PROGRAM

The American College of Chest Physicians, in an effort to advance knowledge of chest diseases and their treatment, has established a Resident Fellowship Program through which medical graduates from other countries can receive assistance in taking postgraduate medical training in chest diseases in the United States. Under this program, the College aids qualified physicians in obtaining suitable postgraduate residencies in cardiopulmonary diseases at accredited hospitals or institutions in the United States. At this time, the College is offering the following fellowship for 1968:

Eudowood Fellowship for Tuberculosis with a grant of $2,500.00 per year for postgraduate training in the United States in tuberculosis. All applicants must be ECFMG certified and the Resident Fellowship Program of the College requires that the candidate be assured of a responsible position in the field of chest diseases when he returns to his own country. Physicians who are interested should write to Dr. Andrew L. Banyai, Chairman of the Council on International Affairs, in care of the Executive Offices of the College, 112 East Chestnut Street, Chicago, Illinois 60611.

CALENDAR OF EVENTS

REGIONAL CHAPTER MEETINGS

Potomac Chapter, Airlie House, Warrington, Virginia, October 15, 1967
Pacific Northwest Chapter, Benson Hotel, Portland, Oregon, November 10-11, 1967
Southern Chapter, Hotel Fontainebleau, Miami Beach, November 12-13, 1967
(The Southern Chapter will meet jointly with the Southern Medical Association. For reservations at the Hotel Fontainebleau, please address your request to the SMA Housing Bureau, P.O. Box 1511, Miami Beach, Florida 33139, giving your arrival and departure dates and indicating that you will attend the College meeting.)

INTERIM CLINICAL MEETING

Warwick Hotel
Houston, Texas—November 25 and 26, 1967
(see program, page 421 this issue)

54th Annual Meeting

AMERICAN COLLEGE OF CHEST PHYSICIANS

San Francisco Hilton
June 13-17, 1968
Combined meeting with American Medical Association - Monday June 17