

## FDA's Drug Monitoring Program for the 70s <sup>1</sup>

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There is much concern today about the quality of drugs in the marketplace and drug product equivalence. Highly placed representatives of the official compendia have recently expressed their views on this topic: Dr. Thomas J. Macek, director of revision for the USP, titled his paper, "Drug Product Equivalence-The Problem, the Challenge and the USP," and Dr. John V. Bergen, National Formulary director and chairman of the NF Board, titled his, "Drug Product Equivalence-Are Specifications Necessary?"

I presume most of you follow the pharmaceutical literature and are familiar with the papers published in the January, 1972 issue of the "Journal of the American Pharmaceutical Association." I believe they have given a valid appraisal of the situation that exists today. It is acknowledged that an equivalence or bioavailability problem exists, but certainly there is not the evidence to establish that as immense a problem exists as some would have us believe. Yet, regardless of the number of products involved, some are of critical medical importance, and it is essential that the problem be delineated and corrected as promptly as possible through the development of adequate standards for assessing drug product equivalence. Committees of both compendia are actively working on the problem as is academia, industry and the FDA. An alternative route that has been given some consideration for correction of the problem is the rigid prescribing by the compendia of compositions and manufacturing procedures.

Much responsibility rests on the Food and Drug Administration with regard to drugs. You, of course, are aware that FDA is the scientific regulatory agency that is charged with enforcing the Federal Food, Drug and Cosmetic Act. This Act, among other things, prohibits the shipment in interstate commerce of adulterated or misbranded drugs and thus is intended to assure quality drugs for the consumer.

Most drugs of greatest therapeutic value are recognized in the current editions of the United States Pharmacopeia (USP) or the National Formulary (NF). These compendia are recognized under the Federal Food, Drug and Cosmetic Act as setting legal standards for drugs. Section 501 (b) of the Act requires that drugs purporting to be those listed in the USP and NF must conform to the standards of strength, quality and purity prescribed therein.

Section 501 (b) further requires that compliance of drugs with the standards set forth in the USP and NF shall be determined by application of the tests and assay methods provided therein, except that whenever tests or methods of assay have not been prescribed in the compendium, or in the judgment of the Secretary of Health, Education and Welfare, they are inadequate, he must bring such fact to the attention of the appropriate compendium officials. If, after a reasonable time, they fail to prescribe adequate tests or methods of assay then the Secretary shall promulgate

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regulations prescribing appropriate tests or methods of assay. To my knowledge this latter portion of Section 501 (b) has never been used. There is, however, effective liaison between the compendia officials and FDA.

Although the Act is intended to assure quality drugs for the consumer, it does not provide FDA with the same degree of control over all classes of drugs. There is a provision for certification of insulin and also antibiotics. This provides for FDA's testing of each batch of these drugs prior to marketing to assure they meet appropriate standards of identity, strength, quality and purity to insure safety and efficacy of use.

After the discovery of insulin some fifty years ago by Banting and Best, the drug was patented and the rights were assigned to the Insulin Committee of the University of Toronto, Canada. Any firm licensed to make insulin was required to have each batch tested and certified by the Insulin Committee. When the patent expired in 1941, Congress felt such a pre-marketing clearance system was necessary. It therefore amended the Food, Drug and Cosmetic Act to require certification of each batch of insulin.

It was a somewhat different situation with respect to antibiotics. When penicillin was first being produced in quantity during the early days of World War II, the entire production was used by the armed forces. FDA developed methods of analysis and specifications of acceptance for such penicillin, and at the request of the War Production Board tested each batch. In 1945, as penicillin became available for civilian use, the Congress again recognized the need for pre-marketing clearance and amended the Act to provide for certification of all batches of penicillin. The Act was again amended in 1947 to require certification of streptomycin, and then again in 1948 to cover chlortetracycline, bacitracin and chloramphenicol. In 1963, the Kefauver-Harris Drug Amendments brought under certification all other antibiotics for human use.

The requirements of the antibiotics certification system are set forth in Section 507 of the Act and in the Regulations. Many of these requirements are quite similar to the New Drugs requirements under Section 505. Before any certifiable drug may be distributed legally, its sponsor must demonstrate its safety and efficacy. He must further provide data on the manufacturing process, assuring that the product will be uniform from batch to batch, as well as specifications for all raw materials used, and a description of adequate tests and methods of assay to determine compliance with proposed standards of identity, strength, quality and purity. The stability of the product must be determined, and each certified preparation must bear an expiration date based upon results of prolonged testing of the drug under normal conditions of storage.

Data submitted by the sponsor is reviewed by scientists in the National Center for Antibiotics Analysis. Tests and assay methods are validated by applying them to samples of the product; with this double-checking, no situation can arise wherein an inappropriate additive interferes with the prescribed method.

Any problem areas must be resolved before a regulation for the drug can be issued. When all is in order, the standards and specifications, the tests and assay are incorporated in a monograph

and published in regulations providing for certification of the product. These provide realistic criteria for quality control and are FDA's yardstick for batch certification.

Mass production techniques have been used by NCAA to increase efficiency in analyzing the large volume of samples. More recently automated systems have been developed to perform many of the repetitive analytical techniques.

There are no provisions under the Act for pre-market testing of other classes of drugs by FDA (except new drugs). Furthermore, with these other classes the number of inspections and batches analyzed is limited by resources available to FDA. This is in contrast to the certification programs which are self-sustaining.

With its limited resources, FDA relies on a combination educational, inspectional, analytical and defect reporting program. I would like to discuss each of these rather briefly, then discuss in some detail some findings from the national surveys carried out at the National Center for Drug Analysis at St. Louis.

Considerable emphasis has been placed on the educational program. We feel that good communication with the drug industry is important. During the last several years FDA has participated with industry and academia in a number of seminars and workshops on Quality Assurance in Drug Manufacturing. This was, and will continue to be, a cooperative in-depth effort aimed to achieve universal compliance with a fundamental provision of the Kefauver-Harris Drug Amendments of 1962. Section 501 (a) (2) (B) of the Food, Drug and Cosmetic Act states that a drug is deemed to be adulterated if "the methods used in, or the facilities or controls used for, its manufacture, processing, packing or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

The Good Manufacturing Practice Regulations implement this provision. They are thus the center of workshop discussions of the problem of attaining unquestioned drug quality through compliance with the current GMP Regulations. Although these regulations were revised in February of last year to improve clarity and specificity, many terms are not defined. The workshops provide the opportunity to discuss the meaning of such terms and freely exchange information. Self-inspection by the manufacturer is encouraged. Let me emphasize that all drug manufacturers are urged to participate in this program.

Many drug manufacturers are operating in conformance with current good manufacturing practices. But experience shows that this is not true for all, and an educational program alone is not sufficient to assure quality drugs. FDA therefore has a number of ongoing surveillance/compliance programs designed to help assure that only high quality drugs reach the consumer. These programs are periodically evaluated and revised or expanded to make use of latest scientific information and to improve coordination, thereby making more effective use of limited resources.

Many of you are undoubtedly familiar with FDA's inspection program in which the routine inspection of drug manufacturing plants is programmed and carried out by the 19 FDA District Offices located in major cities throughout the nation. Each District Office is responsible for inspecting manufacturers in its District, and samples collected during the inspections or as follow-up are analyzed in the District laboratory. These inspections are designed to reveal whether a plant is operating in conformity with Good Manufacturing Practice Regulations. Any deviations found are called to the attention of the manufacturer and steps are taken to remove violative products from the market. Avenues open to FDA to effect corrections are recall, seizure, prosecution or injunction.

As a part of FDA's educational program the Division of Industry Liaison in the Office of Compliance is continuing to publicize to the industry selected case histories of drug recalls as a means of pointing out deviations and failure to observe good manufacturing practices.

Another monitoring program, the relatively new Drug Product Defect Reporting Program, is jointly sponsored by the American Society of Hospital Pharmacists, USP, and FDA. This is a voluntary program in which hospital pharmacists across the nation report defects which they encounter in drug products, their packaging, and their labeling. In the first nine months of this program we have received over 1,200 reports. Since these reflect the observations of professionals, the pay-off rate is quite high.

As an example of things being reported, a pharmacist received a mailing from a company trying to sell convenience containers for nitroglycerin tablets. These were plastic containers made to look like a ballpoint pen. The pharmacist questioned the suitability of this container, and subsequent tests by FDA proved that his suspicions were well founded. The nitroglycerin migrated into the plastic itself causing the tablets to deteriorate in potency at a rate of almost 50% per day.

Many of you are probably aware of this recall. The success of this program has prompted the initiation of two related programs on a pilot basis. The first is an extension of the Hospital Pharmacy Reporting System to community pharmacies in four states. This program is intended to provide information about OTC products as well as prescription drugs. The other pilot program is with the American Nurses Association. Nurses have a unique opportunity to observe problems associated with the administration of drugs. For the first time we are attempting to take advantage of this opportunity in a systematic way.

Now I would like to share with you some of our experiences at the National Center for Drug Analysis in St. Louis. The retail-based prescription drug program initiated when the Center was started in February, 1967 provided for collection of unopened containers at retail and hospital pharmacies located in major metropolitan areas throughout the United States. Although this program provided valuable information on the quality of drugs at the retail level, it became evident that a formulator-based program in which samples of selected categories of drugs are collected from the formulator, branch warehouse or major account had a number of advantages. Under this program, problems are revealed before entire distribution of the drug is made, depth of sampling can be readily controlled, and it provides for more efficient utilization of inspectional time.

In November 1969 we, therefore, changed over to the Formulator-Oriented Rx Drug Study (FORDS) Program. Under this program, samples are collected at the manufacturer's plant, if possible, by FDA District Inspectors and forwarded to the Center where adequate testing is done to determine whether the product meets official requirements. Automated systems are used extensively and we have been doing individual tablet or capsule assays on all samples. This has produced some reassuring results but also some very interesting and disturbing results, including the well publicized problem with Digoxin tablets.

In this program, 20 of the 32 firms sampled produced batches that failed content uniformity test. In one sample we found tablets containing twice the declared amount of Digoxin together with a large number of tablets containing 60-70% of the declared. A number of other batches were nearly as bad. Of 69 batches sampled, 33 or 47.8% were out of compliance on content uniformity. Yet the major manufacturer, holding an estimated 86% of the market, had a defect rate of zero.

Because of the breadth and seriousness of the problem, FDA arranged for all firms manufacturing Digoxin (except the major manufacturer) to participate in a voluntary certification program beginning in October of 1970. The program provides that after each batch passes the firm's quality control tests it will be sampled by FDA and tested at the National Center for Drug Analysis, prior to shipping the lot. When a firm produces four consecutive batches without defect it is released from the certification program.

Several firms promptly improved their procedures to the point where they are producing Digoxin tablets reliably and have been released from the program. Yet, through last year, the overall defect rate of batches from the remaining firms was about 32%. This year to date, however, only one firm has submitted defective batches and that firm is now under a permanent injunction. I emphasize that under this program defective batches have not been shipped and, to our knowledge, all Digoxin sold in the United States has been fully in compliance with compendial standards since the program began in 1970.

The current status of the original 44 manufacturers of Digoxin is as follows: Ten firms have been released from the certification program after having made 4 consecutive batches without defects. Ten firms are no longer making Digoxin (6 because they have dropped the product from their line and 4 because they have gone out of business entirely). The production of the remaining 24 firms is very low and, with the exception of one firm, none has submitted defective batches since the first of the year.

Although it appears the problem with Digoxin is resolved we are disturbed that drug manufacturers in this country consider critical prescription drugs as marketable which are in fact defective in more than one third of the cases. This reflects both extremely poor manufacturing practices and quality control. This is causing us to carefully reevaluate our compliance efforts in this area.

A similar program has been in effect for Digitoxin since March, 1971 and the results are quite similar.

There have been serious problems with several other drugs. A retail based study of nitroglycerin tablets conducted during 1968-69 revealed problems in manufacture and also old stock on the shelves of pharmacies. Defect rate was 3.4%. Defects included potency (both subpotent and superpotent), disintegration, weight variation, and content uniformity. Defective batches were called to the attention of the manufacturer and removed from the market.

Some manufacturers have studied both tableting and packaging and storage of nitroglycerin tablets in an effort to correct their problems. To correct current packaging practices FDA recently issued a Proposed Statement of Policy directing that nitroglycerin for human use be packaged in glass containers with tightly fitting metal screw caps and with no more than 100 dosage units per container; that the labeling include prominent warning that the drug be stored in a cool place, be dispensed only in the original unopened container, and that the tablets be kept in the original container and be closed tightly immediately after use. The USP is likewise proposing to modify the packaging and labeling requirements for nitroglycerin tablets in an Interim revision announcement.

We now have a nitroglycerin survey under way at the Center to determine both quality and stability of current production. We have found defective batches from three of the six manufacturers sampled to date. In a total of 40 batches analyzed, 5, or 12.5%, were found out of limits. Nitroglycerin in individual tablets ranged from 32 to 157% of declared. There have been reports that nitroglycerin migrates from tablet to tablet during storage and becomes unevenly distributed. The storage study is not yet far enough along to report on this.

Serious problems were also revealed in a study on ethinyl estradiol tablets last year. Of 15 batches sampled, 4, or 27% failed to meet requirements. This involved 4 of the 7 firms sampled. Analysis of 90 tablets from one batch showed a range from 35 to 252% of declared, with an average of 99.4% of declared. Eleven of the 90 tablets contained less than 50% of declared and 15 contained more than 150%.

The defect rate in the categories we have been discussing indicates inadequate quality control by a number of manufacturers to assure the quality and integrity of the finished product. The adrenocorticosteroids study which we are just completing is the first category of drugs requiring dissolution testing that we have covered. It is showing a substantial number of batches failing to meet this test requirement. The test was included for the first time in the monograph for Methylprednisolone Tablets in NF XIII and in the monographs for Prednisone and Prednisolone Tablets in USP XVIII. Batches from approximately one-fourth of the firms manufacturing Prednisone and Prednisolone sampled failed to meet the requirements. All samples of Methylprednisolone Tablets (manufactured by one firm) met requirements.

Looking at some of the more reassuring results, no defects were found in 6 of the 18 categories of drugs studied. This is in marked contrast to results found in some of these categories in earlier studies. Survey results show other categories are generally of good quality with only a few batches slightly beyond limits.

The number of quality control tests required to assure compliance has increased to the point that it dictates accelerated use of automated equipment and computerized systems. At the Center, a

medium sized computer is being interfaced with instruments which will increase efficiency and permit us to expand appreciably our ability to collect, process, and interpret data from automated systems.

We recently issued a "Drug AutoAnalysis Manual" of methods used at the Center and elsewhere. A limited number of copies are available. Persons who wish a copy should submit their request on company or university letterhead to the Division of Industry Liaison, Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20852.

In summary, FDA has a number of activities aimed at assuring quality of marketed drugs. The insulin and antibiotic certification programs give greatest assurance of drug quality. The general approach of National Surveys as carried out at the National Center for Drug Analysis with automated techniques has also proved very effective. This program is being expanded to include additional categories of drugs and to improve coordination with other FDA programs. It is the purpose of FDA to work with industry to help assure quality drugs for the consumer.