Certification of Insulin

By R. LORIMER GRANT, Ph.D.

Correct dosage is probably more critical for insulin than for any other drug. Most persons with diabetes must take insulin every day, usually injecting it themselves. A dose that is too small may lead to diabetic coma and even death; an overdose may lower the blood sugar to a level that results in an insulin shock. There are about one million known diabetics in the United States today.

These facts explain the public health importance of the Food and Drug Administration's insulin certification program, which is designed to insure, to the extent possible, that every batch of the drug will be safe and effective when used according to directions.

Insulin was the first drug to be certified by the Food and Drug Administration. Certification was not a new procedure—it had been applied to coal-tar colors for many years—but its application to drugs was new when Congress enacted the insulin amendment in December 1941. This amendment prohibits distribution of any batch of an insulin-containing drug until a certificate has been issued stating that the batch is safe and effective.

History of Insulin Control

The need for special control for insulin by the Food and Drug Administration arose from the expiration, on December 23, 1941, of one of the insulin patents. Until then, the manufacture of insulin in the United States was regulated by the Insulin Committee of the University of Toronto. Banting and Best had given the patent rights of their discovery to the university, and the university's Board of Governors had then taken out the first insulin patents and set up the Insulin Committee to administer them. The privilege of using these patents, and others subsequently administered by the Insulin Committee, was granted to several manufacturers under licensing agreements.

The purpose of the licensing agreements was to make available insulin-containing drugs of uniform and dependable potency at a minimum cost to the user. The potency of each lot of insulin was established on the basis of biological assay in two independent laboratories. The manufacturer was required to make his own assay of a lot and then to submit a sample of the lot to the insulin control laboratory in Toronto, where a second assay was made. As a further check on uniformity of product, the manufacturer was also required to send to the insulin laboratory samples from every batch of finished drug made from a lot of insulin.

The control of potency afforded by these procedures was commendable, and it was appreciated by all governmental agencies concerned with the safety of drugs. In fact, prior to 1941 the Food and Drug Administration did not have facilities for making a reliable assay of insulin potency because these drugs offered no control problems. Moreover, the Federal law was inadequate to deal with insulin drugs. The only procedure available required collection of a sample from interstate shipment, a

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time-consuming assay for potency, and then legal action to prevent further distribution of any drug found to be unsafe. This procedure could result in grave consequences for the consumer.

As the expiration date of the patent approached, several groups, particularly the American Medical Association and the Board of Trustees of the United States Pharmacopeia, sought means to continue the special type of control for insulin that had been provided by the Insulin Committee. E. Fullerton Cook, the director of revision of the pharmacopeia, brought the problem to the attention of the Food and Drug Administration in connection with the drafting of a monograph for insulin injection which was to be admitted to the pharmacopeia after the product patent expired. The Commissioner of Food and Drugs, Walter Campbell, proposed that the pharmacopeia set up an insulin board and establish a laboratory for the testing of the drugs prior to distribution. This plan, similar to that for antianemia preparations, was rejected by the Board of Trustees of the pharmacopeia. Instead, it suggested that the monograph for insulin injection carry a requirement that no lot be released until certified by the Commissioner of Food and Drugs. This proposal was not adopted because it could not be enforced under existing law, but it served to introduce a new idea for Federal control of drugs.

To provide a legal basis for certification, new legislation was needed. Identical bills providing for the certification of drugs composed wholly or partly of insulin were introduced in the House of Representatives on December 16, 1941, and in the Senate on the following day. The bill was passed by the House on December 18 and by the Senate on December 19, and was signed by the President on December 22. This law amended the Food, Drug, and Cosmetic Act of 1938 to require that: (*a*) all insulin-containing drugs be certified before distribution, (*b*) regulations be promulgated by the Administrator of the Federal Security Agency providing for this certification on a fee basis, and (*c*) prior to actual certification of batches, those drugs tested and released by the Insulin Committee be released for distribution.

The Insulin Regulations

The procedure for certification of insulin drugs is described in regulations published in the Federal Register. The original regulations appeared February 6, 1942. These have been amended as new drugs have been added or as experience has dictated.

All the insulin regulations have been drafted in collaboration with the manufacturers of insulin and with the advice of the Insulin Committee of the University of Toronto. They provide for a continuation of the two-assay control of the potency of each lot of insulin and for the examination of samples from every finished batch by both the manufacturer and the Food and Drug Administration. The tests and methods of assay, as well as the standards to be met, are largely those suggested by the manufacturers of insulin. In other words, the industry sets its own standards, and the Food and Drug Administration enforces them.

The regulations require that the manufacturer do the following in order to have a batch of a drug certified:

1. Describe the production facilities and the controls used to maintain identity, strength, quality, and purity of each batch of drug.

2. Submit to the Food and Drug Administration for its approval a sample of the insulin to be used in the batch before he submits a batch for certification. With this sample he must submit a trial dilution of the insulin and the results of his own biological assay of the insulin. He may also send the results of a biological assay made in the laboratory of the Insulin Committee.

3. If the batch is to contain protamine or globin, obtain approval from the Food and Drug Administration of the ingredient to be used.

4. If the batch is to be protamine zinc insulin, globin zinc insulin, isophane insulin, or lente insulin, obtain approval from the Food and Drug Administration of the trial mixture which will serve as a pattern for future batches of the drug.

5. Submit samples and the results of tests of the finished drug to the Food and Drug Administration.

In administering the provisions of the regu-

lations, the Food and Drug Administration must do the following:

1. From time to time, inspect the factories making insulin-containing drugs, with special attention to the facilities, procedures, and controls applied to insulin.

2. Analyze samples submitted in connection with a request for approval, make biological assays to determine potency, review protocols of the manufacturer and of the Insulin Committee's testing laboratory, and notify the manufacturer of approval or refusal to approve the material for use in making batches of an insulin drug. If approval is refused, the Commissioner of Food and Drugs must tell the manufacturer the reasons.

3. Test samples from every finished batch of an insulin drug before issuing a certificate stating that the batch is safe and effective. These tests always include a determination of nitrogen content, which is an indirect measure of potency, and a check on sterility.

Since the manufacturer has usually completed all of his tests before submitting a sample, refusals to approve or certify are rare. Most cases of refusal to approve have involved the trial mixtures of the slow-acting insulins. The samples submitted in these cases failed to meet all the standards established to insure uniformity in the type and duration of action of the drug. An adjustment in the proportions of ingredients has usually produced a mixture that could be approved. Certification was refused for one batch of protamine zinc insulin that was found to be more alkaline than the permitted limit. This condition was evidently caused by traces of the washing solution used to clean the vials. Samples of one batch contained viable organisms, but the manufacturer found the contamination after submitting the sample and did not complete his request for certification.

As a measure of the effectiveness of control by certification, the Food and Drug Administration investigates every complaint concerning a certified drug. No complaint has been found to be due to a contaminated or faulty batch of an insulin-containing drug. All partly used samples that have been found to contain viable organisms appeared to have been contaminated by the user. No complaint of lack of potency has been substantiated. Recently, some patients ignored the label warning and used protamine zinc insulin which had become granular. Samples of the same batch kept in proper storage had a normal physical appearance. We believe that all certified insulin-containing drugs are safe and effective when they are used according to the directions on the labeling.

Organization of Control

The responsibility for certification of insulin has been delegated by the Commissioner of Food and Drugs to the Division of Pharmacology and specifically to the Insulin Branch of that division. The staff of the Insulin Branch consists of the branch chief, one chemist, two laboratory technicians, and one secretary. Laboratory facilities include one animal room, where the rabbit colony is housed and the bioassays are conducted; one chemical laboratory, where routine tests of samples are made; and the combined laboratory and office of the branch chief. These laboratories are equipped and maintained and the staff of the branch is paid from the fees collected from the manufacturers who use the certification service.

The fees for the different services vary, but the major portion of the income is from the fixed fees for certification of batches of finished products. The fee for a single batch is determined by the number of samples submitted for test. At the present time, the cost to the manufacturer is $50 for batches containing up to 50,000 vials plus $10 for each additional 10,000 vials in the batch. Any excess of income from the fixed fees over the cost of maintaining the service is refunded. Some fees depend upon the cost of the services. For services that require the use of the animal colony, most of the fee is attributable to the cost of maintaining the colony. For instance, the present cost of a biological assay for potency is approximately $1,200, more than half of which is for maintaining the animal colony.

Biological Assay Procedures

The most important test required for the certification of insulin is the biological assay for

potency. The potency may be determined by a number of methods, all of which involve a comparison of the drug being tested with a standard insulin. The methods used by the Food and Drug Administration have been the variations of the rabbit method currently official in the United States Pharmacopeia. The U.S.P. XII method required almost 1,000 determinations of blood sugar and two 5-day work weeks for completion. The test now official (U.S.P. XV) is greatly improved. It can be completed in 1 work week, and the confidence limits of the results can be calculated. It is possible, when the responses of the animals are very uniform, to make only 96 blood sugar determinations for a suitable assay, but the usual number is nearly 300.

As with all biological assays, the reliability of the assay of insulin depends on the extent of variation in response of the animals. To obtain the best results, unsuitable animals must be discarded from the colony. It is therefore essential to have an animal colony that is used exclusively for the assay of insulin and to maintain it in readiness to assay any sample submitted. A chemical method for determining potency would reduce considerably the cost and probably would increase the precision of the results, but our knowledge of the chemical structure of insulin indicates that some entirely new technique will be needed before we realize this goal.

It may appear that certification, while affording maximum protection for the user of insulin, substantially increases the cost of this essential drug and thereby adds to the burden of the consumer. However, we have calculated that the total fees collected by the Food and Drug Administration for insulin certification since the beginning of the program average less than three-tenths of a cent for each vial certified.

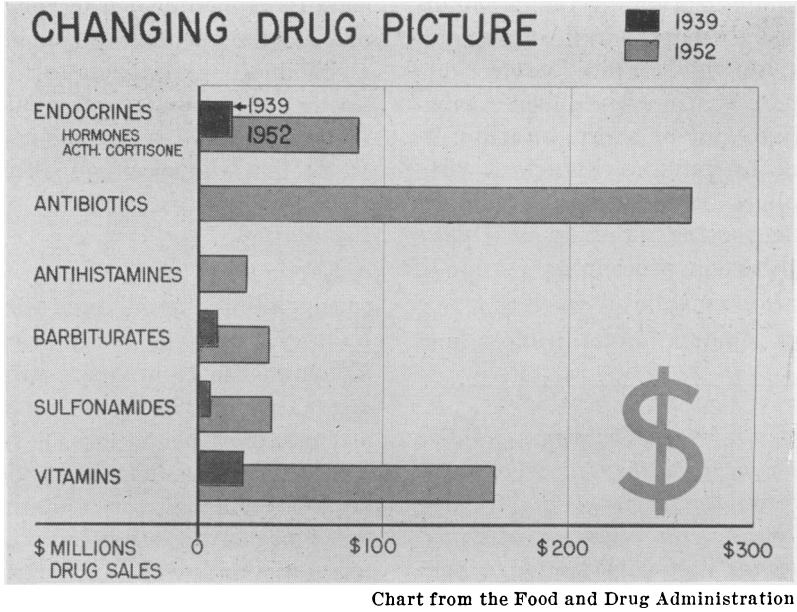

Chart from the Food and Drug Administration

Drug sales reflect advances in biochemistry. Approximately half of the total dollar value of prescriptions written today goes into antibiotics unknown in 1939. The sales of endocrines have grown from $10 million to more than $90 million. Antihistamines, unknown in 1939, have sales exceeding $25 million. Barbiturate sales have more than tripled. Sulfonamides have multiplied eightfold, and vitamin sales have increased about sixfold. Drug consumption as a whole has greatly expanded.