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The complexities of modern scientific knowledge have vastly increased the requirements for the clearance of an animal drug for market. All such drugs, which include those for poultry, are subject to the regulations of the Food and Drug Administration (FDA). The data obtained in the development studies must convince the FDA examiners that the drug is both safe and effective. To accomplish this, numerous disciplines are involved, such as parasitology, microbiology, pharmaceutical formulation, nutrition, animal management, organic chemistry, analytical chemistry, biochemistry, pharmacology, pathology, veterinary medicine, chemical engineering, and statistics. Thus, the desired product can only be obtained by a team approach. In our laboratory there are four teams involved; the first finds an effective drug, the second evaluates its safety, the third evaluates its action in field tests, and the fourth produces the drug in quantity.

Product development is expensive, yet new products are essential to a dynamic industry. Because of the costs, all product development must be carefully evaluated by management. The market is determined, selling price estimated, and the cost of research, development, and production evaluated. Only then can a decision be made concerning the potential of the product. Some products, such as those for poultry, must be marketed at a very low cost, for the total cost of medication and vaccination should not be greater than three cents per broiler chicken.

The challenge of drug development is that it is the result of someone's idea. As the idea is developed, other ideas occur so that one is working in a thought-provoking environment and continually subjected to the stimulus of problem-solving. There is a great satisfaction when the product is marketed.

The initial testing of a substance or compound may be simply a blind screen, that is, testing the material for activity on the basis of its availability. However, in the writer's experience, he selected first those compounds which, from their chemical structure and from knowledge of the scientific literature, he judged to be most likely to have activity. The organic chemist also enters into this picture, for he may have conceived of a chemical, synthesized it, and submitted it for testing. Once some degree of activity has been determined, then the biologist and chemist can work together in molecule manipulation, that is, changing the position of a moiety or substituting other moieties on the basic

structure. For example, when the writer was doing this work and found activity for organotin compounds as anthelmintics, he examined 125 of these compounds. The best of these was selected for a product, and excellent patent coverage was obtained for the series. Other biologists then tested a number of the compounds for activity against other disease-causing organisms.

The next step is the establishment of all ways in which the compound may be used, i.e., for treatment, for prevention, administered as a tablet, in the feed, in the drinking water, or by injection. Not only must the amount be established, but also the length of time it will be administered. Since few drugs are administered as the compound *per se,* it is necessary to formulate it into a product. If it is to be a tablet, suitable binders or other ingredients must be found. If it is to be administered in drinking water, it may have to be incorporated with solubilizers or pH controlling agents. A product to be mixed in feed usually consists of the compound and some suitable feed ingredient which will permit thorough distribution in the final feed. An injectable product must not be more than transiently irritating. In each dosage form, the effectiveness of the product must be clearly defined.

The studies to this point have required a considerable quantity of compound. Usually the organic chemist has been supplying it from syntheses in his laboratory. This has provided the opportunity to try different production procedures and from this experience he has reached a decision as to the most economical method of production in the chemical plant. This work has also permitted better definition of the physical and chemical properties and methods of purification. Identification of the contaminants which may be present is also important.

At this point, another team takes over the production of the compound. This team consists of production chemists and chemical engineers who determine how to adapt the procedure recommended by the organic chemists to the production facilities. This is usually done through a pilot plant process where it is determined what effects reaction conditions have upon yield when pound batches of the chemical are produced. The quality of the chemical must be continually checked. As experience is gained, the type of equipment required for larger batches and the economics of the process are worked out. These studies finally permit the definition of the specifications for the compound, that is, its purity, and physical and chemical characteristics for identification.

In our institution, analytical chemistry is tied in with the safety team. These chemists have been involved in developing a method of analysis and the more specific the method, the better it is considered to be. Three methods of analysis may be necessary, one for the compound itself, one for the compound incorporated in the product, and one for the final dosage form if that form is feed or drinking water. The last method requires the greatest sensitivity because the dosage may be as low as 50 ug per gram of medium. The final dosage form method of analysis must also be studied for possible interfering substance, such as

other drugs which are used in feeds, which may be included by chance or accident. This knowledge is very helpful in the quality control of the final dosage form. The first two types of methods are supplied to the quality control section of the production team and the third is made ready for the eventual customer.

When methods and formulated product are available, the analytical chemist initiates stability studies on the product and, if applicable, the final dosage form in feed or drinking water. These are subjected to various environments and analyses made at definite intervals over at least a six-month period to determine whether changes in quantity have occurred. Also, many feeds are pelleted, so it must be shown that this process does not change the content of the compound.

When sufficient compound is available and the dosage has been established, safety studies are initiated in animals. The first of these are designed to determine the safety of the product for the animals on which it is to be used. The types of safety tests which may be done are: acute toxicity, which are short-term; subacute toxicity, which are ninety days in duration or for the lifetime of a short-lived animal (broilers, turkeys); chronic toxicity, which are two-year tests; and reproduction tests to ensure that the compound has no effects on this phase of life. In most of these tests, it is desirable to determine the maximum dose which has no harmful effect (the no-effect dose) and the maximum tolerated dose, or that dose which harms, but is not lethal.

Acute toxicity studies are done primarily on compounds in products which are used for treatment of disease and particularly those which will be used for only a few days. This test involves the determination of the single oral dose which will be lethal to 50 per cent of the test animals ($LD_{50}$). The acute toxicity of compounds to be given to large animals is determined in laboratory animals. The $LD_{50}$ is used because it is the most easily reproduced and is actually established by means of a statistical manipulation. From this a therapeutic index is derived, that is, the ratio between the $LD_{50}$ and the therapeutic dose. The greater the ratio, the greater the probability of safety. It is also very helpful if one can determine by this test the organs most affected by an excessive dosage.

The subacute toxicity test is of particular value for compounds which are given for weeks or months. Such compounds are usually incorporated in disease-preventive or growth-promoting types of products. In this test, a series of dosages covering a wide range are continually administered and are started during the growth phase. The minimum length is ninety days, but it may be extended to the normal market age of the animal. Sufficient numbers of individually housed animals of both sexes are used in each dose level to permit a valid statistical evaluation of effects on growth and feed consumption. During the test, hematologic studies are made periodically and a number of other biochemical tests may be conducted. All animals dying during the test are examined, and at the end of the test all are killed and examined for gross pathology. Samples of approximately

thirty tissues are taken for microscopic evaluation by a pathologist. The product is considered to be safe for the animals if the maximum no-effect dose is at least three times the use-dose of the compound.

Because the safety for man is part of the evaluation, the same type of test is also conducted in rats or mice and dogs. These tests are ninety days in duration. If the maximum no-effect dose and the maximum tolerated dose are approximately the same in the two species, toxicologists assume that man can detoxify the compound in approximately the same manner and a potential hazard for man can be established.

During this time, biochemists have also been at work to determine whether the compound is metabolized by the animals and, if so, what the principal metabolites are. A method of analysis for these must be developed so that the amount of residue in the major consumable tissues can be determined. The sensitivity of the method depends on the toxicity of the drug. A drug which has a wide margin of safety, i.e., a low order of toxicity, does not require as sensitive a method, while one with a narrow margin of safety requires greater sensitivity. A rule of thumb in our laboratory is sensitivity and accuracy to less than 0.1 ug per gram of tissue. Methods 10 to 100 times this sensitivity are in use today. The sophistication of the method usually involves some type of chromatography and the use of sensitive electronic devices, e.g., gas chromatograph, spectrophotometer, polarograph. When the method is available, then the rate of disappearance of the residue following the withdrawal of the drug is established. This provides evidence for determining how long before slaughter for human consumption the drug must be withdrawn. If applicable, the occurrence of the residue in milk or eggs is also made and if any is found, the product can be used only in such a manner that the milk or eggs containing residue will not be consumed by man. In this manner, man is protected from a possible hazard in his food.

If a residue exists and it is desirable to give the product until slaughter of the animal for human food, then present FDA requirements are that the compound must be subjected to a chronic toxicity study in rats or mice and dogs. In our laboratory, in addition, we conduct such tests in chickens. Except for dogs, the size of each treatment group must be large enough to permit adequate data at the end of the test for statistical evaluation. A current test was started with a total of 1,200 mice and another test with 400 rats, each individually caged. The dosages used may be governed by the highest tissue residue found while the animals are receiving medication. The residue in meat may be considered to be safe for man if 100 times its quantity is safe for the test animals when given throughout the two years of test. Food consumption is measured throughout the test because it measures the dosage since the compound is incorporated in the feed. Body weights are taken at weekly or biweekly intervals. Periodic hematologic examinations are performed and enzyme studies may be conducted. Each animal which dies must be examined at post-mortem and tissues taken for histologic examination. At the termina-

tion of the test, all of the survivors are killed, examined for gross pathology, and tissues from a proportion are subjected to microscopic examination by a pathologist. This type of test also determines whether the compound may be cancer-inducing in the rodent.

The fourth team involved in the development of a drug is the clinical team. Before the drug can be cleared, it must be subjected to testing in the field. This cannot be done until effectiveness has been shown, safety studies have been completed, and the tissue residues and the rate of their depletion established to the satisfaction of the FDA. Thus, when the animals go to market, there will be no potential hazard for man. The purpose of this testing is to determine both the safety and effectiveness of the use dose under diverse conditions. To accomplish this, the testing is carried out in about half a dozen different geographic locations during different seasons of the year. A considerable number of animals are used at each location and in the different seasons. With broiler chickens, this may total to several hundred thousand birds. During the course of these tests, periodic examinations are made of the group undergoing medication for effectiveness of the drug and for any unpredicted reactions. If the animals are slaughtered for human consumption, they are followed through the packing house and the carcasses examined. If the product is a disease preventive, it must be shown that the test animals were exposed to the disease. A product successful in these tests should be successful on the market as far as safety and effectiveness are concerned.

The extensive and intensive work required for the development of a product for market clearly shows why a team approach is the only practical approach. Judicious management procedures must coordinate and correlate the many scientific disciplines involved. One important aspect not previously mentioned is the necessity of clear, concise, well-organized and readily understandable reports of the testing so that others, particularly the FDA officials, can easily conclude whether the product is safe and effective. It should be readily understood that a number of years are involved in completing the development of a drug. If no serious difficulties are encountered, the shorter-term phases of development can be completed in approximately two and a half years. With luck and good planning, the entire testing takes four years, but our experience has shown that five years are frequently required.

The whole procedure of drug development is very challenging. When it is accomplished, those involved derive much satisfaction, particularly when the marketing personnel are successful in selling the product and the need of a customer is fulfilled. One also has the satisfaction of knowing that he has made a contribution to the food supply for man, a contribution which by modern methods of evaluation will not add to the potential hazards encountered in man's daily life.