The Development and Introduction of New Animal Drugs

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The main consideration of this article regards the development of agents for use in animals which may be used for human food, i.e., cattle, swine, sheep and goats, poultry and horses.

If the agents are to be administered in other animals (not for human consumption) then some of the tests and studies mentioned in the following will not be required.

The pursuit of identifying and developing new drugs is a multi-disciplinary effort generally conducted by fairly large organizations, which also are interested in commercial production and distribution of such products. This research work usually requires chemists, pharmacologists, microbiologists, statisticians, physicians, veterinarians, toxicologists, pathologists, technical assistants and others to develop and carry out the scientific aspects of the investigations. On the economic, marketing and use aspects; market analysts, financial managers, distribution and scientific information personnel work with veterinarians, physicians and other health care/animal production personnel to evaluate and develop marketing capability of products for use in the prevention and treatment of disease conditions in man and/or animals. Physicians and veterinarians, assisted by statisticians, monitor ongoing use of products in man and animals respectively.

Source of Agents

These usually originate in a chemical or biological laboratory. The individuals involved in identifying the substance have some idea of their pharmacologic or biologic activity. Such information generally is discussed with individuals who are prepared to conduct preliminary tests in one way or another to demonstrate or confirm the hypothesis.

Many chemical compounds have been and are being synthesized or modified that have potential useful application. Needless to say some of these also have undesirable characteristics such as toxicity in a biological system and thus are not useful in the medical fields. This aspect must be determined early in the investigation for economic reasons. Also, cost of the substance should be estimated before large scale studies are initiated for potential new animal drugs.

Screening Tests

When it is determined on a theoretical basis that a compound or substance has the potential for use, preliminary tests are initiated to demonstrate pharmacologic and/or biologic activity.

Some of these tests may be carried out by *in vitro* tests, i.e., antibiotic sensitivity tests with certain pathogenic organisms. When a compound possesses potentially useful pharmacologic activity, then such trials are conducted, i.e., anesthetic agents. If results are favorable then *in vivo* trials are conducted. If these trials appear favorable, it is then important to determine the potential toxic effect, at least in a preliminary way, such as the LD 50, and/or gross harmful effect. Also, preliminary potential residue status must be determined at this early stage.

All of these tests usually are conducted in small laboratory animals because of expense and available supplies of compound(s).

Utility Tests

In the development of animal drugs it is permissible and feasible to conduct trials to determine whether the substance possesses the desirable prophylactic or therapeutic effect in the target animal. This can generally be done by infecting, or acquiring infected animals, or demonstrating the desired pharmacologic action in target animals.

However, such test animals must be considered as laboratory animals and may not subsequently be used as pets, work animals or for food, since such uses would be inconsistent with the regulation governing such investigational drugs and animals and there is no knowledge at this time regarding the fate of the test compound in milk, meat or eggs (human food).

In this regard, it is possible to proceed more rapidly in developing animal drugs than those being investigated for use in humans.

At this stage, dosage formulation and stability studies also are initiated since these too are very important in the development of drugs to be used in a variety of animals under varying conditions.

Toxicity Tests

There are several types that must be considered, but for animal drugs it is advisable to have some assurance that the anticipated use-dosage is safe in the target animal. Thus preliminary trials usually are conducted before a commitment is made for the large financial investment necessary to develop the information required to prepare the investigational new animal drug (INAD) application. (If the subject drug is to be used only in non-food producing animals, the financial commitment may be dramatically reduced

since at this time, residue studies are not required for this class of animal.)

Information for INAD
Tissue Residue Studies

Since enactment of the 1958 Food Additive Amendment to the Federal Food, Drug and Cosmetic Act–and the 1962 amendments to the Act–the question of drug residue in milk, meat and eggs must be determined and included in the INAD.

Such information can be obtained by the use of radioactive compounds, by chemical assay methods, or in some cases by microbiologic analytic procedures. A comprehensive metabolic profile is now also required.

In such studies the agents must be administered to target animals and in doses in excess of the anticipated use-dosage. If radioactive compounds are used finite information can be determined with a limited number of animals, however, this does not preclude the requirement of also developing a regulatory assay at a later date for consideration in the new animal drug application (NADA). In some instances, it is more feasible to develop a chemical analytic method for tissue residue determination early on instead of conducting studies with a tagged compound. But, under the total residue concept, complete metabolic studies are now required for NADA purposes which must be done with C14 or equivalent types of studies.

Microbiological test methods usually are used for the tissue residue studies when investigating antibiotic substances.

Safety or Toxicity Studies

These are frequently referred to as chronic studies and are conducted primarily with respect to potential effect in humans who will consume food of animal origin (milk, meat and eggs). Such studies are not mandatory at the INAD stage but, as a practical matter, they greatly facilitate agency decisions regarding withdrawal interval and analytical method sensitivity requirements.

These studies are conducted in at least two species of animals (one not a rodent), generally in rats and dogs. The new regulations also require the standard carcinogenicity studies in mice for drugs which are to be administered continuously (for NADA purposes). Additional studies may be required if subject compound is deemed a suspected carcinogen.

These additional studies consist of 90 consecutive days of medication at least in three dose levels (frequently more) to determine the no effect and an effect (toxic) level. Many observations and tests are made on animals during this period to detect drug effect.

At the end of the medication period animals are sacrificed and gross, as well as histopathologic, examinations of tissue are conducted. These studies must include an adequate number of animals for statistical analyses of the results.

Reproduction studies in laboratory animals (rats, mice, rabbits) frequently are conducted at the same time that the above toxicity trials are done, since knowledge of such drug effect in this regard is very important and desired by all concerned.

Efficacy Studies

Data may be included in the INAD indicating that the drug product possesses utility in the target animals; such as prevention, control or treatment of disease conditions or improved feed efficiency and/or rate of gain. Many of these early tests are conducted in suitable test animals with well planned and properly supervised studies so that statistical analysis can be applied and thus meaningful conclusions can be made.

The above safety studies are essential for consideration in filing an INAD to obtain authorization for food use of treated animals. This allows for expanded studies to collect data to prepare the NADA; otherwise, such animals must be destroyed by incineration or burial. In addition, and perhaps more important, these expanded studies permit the sponsor to decide whether a further commitment of funds is to be made for the additional studies that are required. At this point in time, all members that have decision-making responsibilities must be fully informed in order to make a reasonable decision to proceed or to discontinue the project. This truly is an intradisciplinary activity.

If and when the Food and Drug Administration grants authorization for food use of the treated animals under the INAD, then expanded studies usually are initiated. Information from FDA often serves as a guide to what is required. Such information frequently is determined in consultations and discussions by knowledgeable individuals familiar with the information in the INAD. Needless to say, it is highly desirable to have this information and understanding confirmed early on so that the required tests and studies can be planned and conducted.

Information for NADA
Additional Efficacy Studies

When the decision is made to file an NADA, additional clinical studies to demonstrate and confirm the previously obtained efficacy studies may need to be conducted. These must be carried out in at least three geographic areas of the country, unless the preparation is to be restricted for distribution in a limited area.

Such studies frequently are conducted on a "blind" basis to eliminate bias in the conclusion. Also, it is highly desirable to have a statistician participate in the preparation of the protocol for such studies since such personnel will assist in drawing conclusions from the trials. Note that regulations require at least two well-controlled efficacy studies which may be conducted as clinical trials.

Incidentally, these field studies must be conducted by individuals who are familiar with the clinical problems, willing to follow the protocol, prepare

meaningful reports and use the drug product only for the studies as outlined.

Such trials must be reported to the FDA's Bureau of Veterinary Medicine; giving the name and address of the principal investigator, location of the study, number and specie of animals involved, the handling of the animals and products (milk and eggs) during and after completion of the study, i.e., the withdrawal period during which time the animals or their products are not to be used for food.

Drug Resistance Studies

When a new antibacterial drug is under investigation, studies must be conducted to determine whether or not the etiologic agent develops resistance and this resistance in turn is transferrable.

Additional Safety Studies In Target Animals

Additional studies in target animals may be necessary to determine toxic or adverse pharmacologic effect. These may include teratogenic studies in the several species of animals in which the drug is to be used.

In addition, field trials in several locations are required to determine that the use of the new preparation is satisfactory in the usual clinical situations. Here again it is necessary to conduct such trials in a formal manner so that meaningful information is obtained and can be included in the NADA.

Filing the NADA

The new animal drug application must contain detailed information, raw data and summaries of all the studies that have been conducted with the compound or substance. It is important that it is presented in an orderly manner for review by the FDA personnel.

Three copies of the complete application must be submitted to the BVM. There it is assigned to one of the selected individuals who will monitor the review by others in the agency; such as bureau of foods, chemistry and/or antibiotic section as well as a review by other personnel in BVM.

The application must contain full details regarding the:

1. Composition and identity of the drug product.
2. Manufacturing methods for control, including stability data and test methods.
3. Reports on all toxicity and safety tests.
4. Drug residue information and validated analytical procedures.
5. Results of the efficacy trials, with statistical evaluations of the same.
6. Samples of the drug product must be provided if requested by the agency.
7. Copies of proposed labeling.
8. Environmental impact analysis report.

Receipt of the application is acknowledged by the FDA, which then by law is required to act on it within 180 days. (However, this legal requirement is commonly ignored by FDA.)

In most instances during this period questions are asked by the agency which permits final action on the application to be delayed and many times for a long period (years).

When the application is approved a regulation regarding the permitted use of the agent is published in the *Federal Register*, which then is public information. Such regulation is quite specific with respect to claims and conditions of use for the product and also identifies the manufacturer.

Labeling for User

The labeling on containers, packages or inserts provides significant information regarding dosage, administration, precautions and warnings.

Various label sections contain information dealing with the consequences of not following directions, such as adulteration of meat, milk and eggs and damage to treated animal(s).

In the case of drug residues in food animals, the potential danger to human health is an important consideration; as are the legal liabilities of those associated with the illegal use of the product. Legislative and/or administrative action can and will be employed to control residues, if found necessary.

Responsibilities regarding this matter are well described by an article entitled "Legal Responsibilities in Prescribing Feed Additives and Drugs" by Harold W. Hannah, LLD, in the *Journal of the American Veterinary Medical Association*, September 1, 1973.

The preferable way to control drug residues is for those responsible for the use of drugs, i.e., livestock producers, animal industry advisors, veterinarians, and others to do everything possible for proper and approved use and thus to keep potentially harmful residues from occurring in animals destined for slaughter or out of animal products (milk and eggs).

Product labels may also contain warnings about the danger of mixing drug combinations and potential for drug stability problems when products are improperly handled or stored.

Subsequent Procedures

If the preparations are to be used as additives in preparing medicated feeds, the feed manufacturer is also required to file and obtain approval of an application from BVM. Such procedure requires detailed information regarding the preparation and labeling of the medicated feed(s).

Drug Experience Reports

These are required from the drug manufacturers at six month intervals for the first year following the introduction of the products and annually thereafter. These reports are studied by the FDA personnel and used for surveillance of the products in the market place.

Supplemental new animal drug applications usually are made following the initial NADA approval to provide for changes, corrections and additions to the items originally listed. These are considered and approved, with limited exceptions, under the same statutory requirements as the original application.

Summary

The above describes in a general way the various steps followed in developing new animal drugs and to comply with federal regulations. It also lists the various tests and trials to demonstrate safety and efficacy for the same.

In addition, it explains the background for the regulations regarding the use of chemicals, drug products and substances so that they can be employed safely for animals as well as humans who own and consume such animals and their products.

Pentachlorophenol Contamination of Animal Feed

The Food and Drug Administration, along with state and other federal agencies, is investigating new cases of chemical contamination of animal feeds in Michigan.

The episodes came to light earlier this year during follow-up surveys of problem dairy cattle herds from the 1973-76 polybrominated biphenyl (PBB) contamination incident. Thus far, eight herds have been found with significant blood levels of pentachlorophenol, a chemical used as a pesticide and wood preservative.

The contamination could have national implications because of the long and widespread use of pentachlorophenol, also known commercially as Penta and PCP. It has been used throughout the country since the 1930's to treat wood in barns, telephone poles, corrals, pens, fence posts, and feed bunks. It is probably in use on most U.S. farms.

While all eight herds have been quarantined, the symptoms are somewhat incompatible with typical PCP toxicity. Therefore, the impurities found in most commercial PCP also are being examined. These include dioxins and dibenzofurans. While not all dioxins are considered highly toxic, some are thought to be among the most potent toxicants known. Dibenzofurans are closely related to the dioxins. Also being investigated are toxic factors related to organic solvents commonly used to dilute commercial PCP, such as used motor oil.

Cattle can absorb the toxic compounds in PCP orally (by licking treated wood or eating feed that has been in contact with treated wood) by inhalation and through skin contact. The Michigan episodes occurred during the coldest part of last winter in closed barns with little ventilation. The barns all contained PCP-treated lumber, and silage was commonly stored in bunk silos lined with treated lumber.

Problems in the cows included spontaneous abortions, respiratory difficulties, liver and kidney damage, persistent infections, and deaths. All but one of the problem herds have responded well to increased ventilation and other corrective management practices, with PCP blood levels returning to normal for Michigan dairy cattle.

Thus far, tests show no PCP or dioxin contamination in milk from cows with high PCP blood levels, except for one grossly contaminated specimen. Numerous samples of feed, grain, and mineral mix fed to the herds contained PCP, with levels from 0.07 parts per million in a granary sample to 13.77 parts per million in a sample of oats. The feed samples have not yet been analyzed for dioxins. All liver samples from dead cows showed dioxin content, mostly the least toxic octa isomer. But half of the samples contained the more toxic dibenzodioxins as well.

The greatest potential public health hazards of PCP contamination include possible human exposure to such contaminants as dibenzodioxins and dibenzofurans, and the possibility of these toxicants in milk and meat products. For that reason, the U.S. Dept. of Agriculture has contracted with Wright State University in Ohio to analyze milk samples in a nationwide year-long survey. The Division of Veterinary Research in FDA's Bureau of Veterinary Medicine and the Bureau of Foods will analyze milk samples from test cattle fed high levels of PCP and dioxins. Other research is now being planned to investigate further the toxicology of these compounds.

Thus far in the investigations, considerable evidence implicates PCP and its commercial impurities as causes of the problem in the cattle. However, a definitive diagnosis must await the conclusion of the studies.

While it is impractical to test every lot of PCP or PCP-treated wood for impurities, all PCP products should be suspected of containing dangerous toxicants. (PCP-treated lumber may appear lightly or darkly stained. Suppliers normally know whether their products have been treated with PCP.) Exposure of livestock and humans to PCP should be avoided as far as possible. Here are some suggestions for livestock producers:

*Don't permit animal feed to come in contact with PCP-treated wood or other PCP sources.

*Don't permit animals to lick, chew on, or rub against PCP-treated material.

*Animals placed in new surroundings with PCP-treated material should have access to outside lots. Enclosed structures should be well ventilated.

*Read and follow directions carefully when using wood preservatives. Don't use more applications than are recommended and do not dilute PCP with motor oil. Kerosene, however, is an acceptable diluting agent.

*Animals with tissue residues of PCP or dioxins are not fit for rendering, since the rendering process does not break down the PCP or dioxins.

Given the widespread use of PCP, veterinarians should be alert to possible PCP toxicosis in problem herds and report such incidents immediately to the Food and Drug Administration.

July 1977
Bureau of Veterinary Medicine
D.H.E.W. Pub. No. 77-6023 (FDA)

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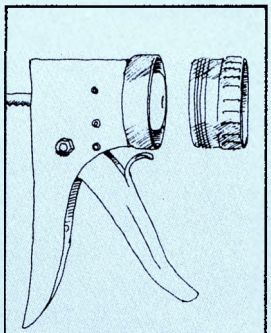

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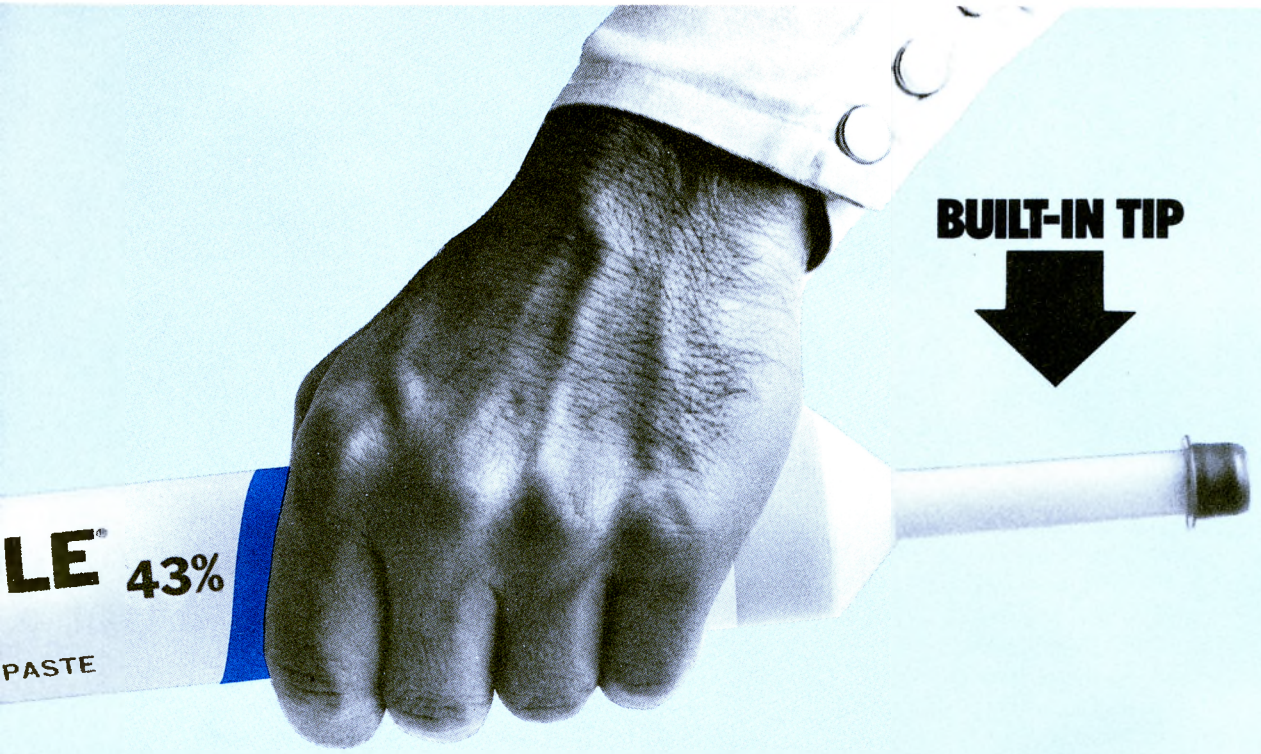

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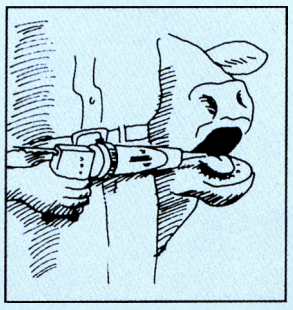

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