Development of Animal Health Products to Comply with World-Wide Regulatory Requirements

Ronald H. Dalrymple*

Introduction

With the current interest in food safety, residues in food and animal welfare, I thought it was important to inform you about the development of animal health products and the regulatory agency requirements that need to be met in order to obtain government approval to manufacture and market a product.

There are four main goals to an animal health industry product research program. The initial goal is to fill an identified market need by discovering new active compounds using basic research, screening and acquisitions programs. Generally, with a food animal health product, there needs to be a potential world-wide market in order to justify the research and development costs which can range into the 10's of millions of dollars. The time from discovery to marketing can also take up to 10 years.

The second goal is to obtain a proprietary position with the new product, be it the compound itself, a unique formulation or a manufacturing process. This means a simple seven letter word "PATENTS." They are the basis of a company's discovery, formulation and process development programs and the reason why so much of our work is "secret." These patents should be filed in the major market countries worldwide to insure adequate protection; however, many countries do not have an adequate patent system and(or) enforcement.

The third goal is to obtain regulatory approval in major market countries. This is the key to the entire process. Many new agents are discovered and patented each year, but only a few wind their way through the entire development and regulatory process. To achieve this goal, the company must convince itself and the government that the product is effective under real-life conditions, is safe for the target animal, safe for the environment, safe for people who handle the drug and, most importantly, safe for people who consume food produced by the treated animal. Furthermore, the company wants to be sure that the product is right for the marketplace. It must be convenient to use and cost-effective to both the company and expected users.

The final goal is to introduce the new animal health product into the marketplace and achieve commercial success.

*R.H. Dalrymple, American Cyanamid Company, Agricultural Research Division, P.O. Box 400, Princeton, NJ 08543-0400

Reciprocal Meat Conference Proceedings, Volume 43, 1990.

Governmental Regulatory Agencies

To begin the discussion, it is important for us to understand a little about the different regulatory agencies involved in approving and regulating animal drugs. For simplification, I will only outline the different agencies in the United States, Canada and the European Community. However, every country has one or more regulatory agencies that deal with animal drugs and for international companies, such as Cyanamid, this means we have many different people and regulations with which we must interact. We have a separate regulatory affairs section which handles most of this interaction. However, the scientific staff are directly involved in collecting the information which goes into a regulatory submission. Each submission contains numerous volumes and many are the size of several sets of encyclopedias. Considerable supplemental information is also submitted during the regulatory review process to address questions and concerns of the reviewers who work for the agencies. In general, the studies we conduct to meet the FDA requirements will also meet the requirements of most other countries. However, efficacy, target animal safety and residue studies will usually have to be conducted in each individual country under "local" conditions.

United States Regulatory Agencies

Let us begin by examining the regulatory process in the U.S. There are three agencies within the federal government which regulate animal drugs. Each one has a different regulatory responsibility. The general categories of animal health products subject to regulation are nutritional feed additives, production-enhancing drugs, therapeutic drugs for disease prevention and treatment, veterinary biologicals (mainly vaccines for disease control) and topical animal pesticides. In the regulatory process of the United States and most countries, drugs in these categories are reviewed by separate sections of an agency or by different agencies. Therefore, their regulatory requirements can differ greatly. Each agency is staffed with scientifically trained reviewers who make the decisions on efficacy, safety, etc. In the U.S., the following agencies are involved in the regulatory process:

Food and Drug Administration (FDA) — Center for Veterinary Medicine approves and regulates animal drugs (both therapeutic and production drugs) and nutritional feed additives.

United States Department of Agriculture (USDA) — regulates the licensing of veterinary biologicals and monitors the use of drugs in food animals. USDA's Food Safety and Inspection Service randomly inspects animal products to monitor drug residue levels.

Environmental Protection Agency (EPA) — regulates and approves topical animal pesticides.

European Community System

In the European Community (EC) countries, the division is slightly different; it is generally divided into feed additive medications and veterinary prescription drugs (including biotechnology products). The EC is moving toward more centralized regulatory procedures in line with the move toward a single Europe in 1992. Currently, each member country has a regulatory body that deals with animal health product approvals. Separate approvals must be obtained from each country. While this system will remain in place for the foreseeable future, there will be a harmonisation of registration procedures by the member states. To obtain EC approval, the first step is to receive approval in one member state. This country then becomes the "sponsor" country and presents the application to the appropriate Directorate-General Commission for review by an external, independent expert committee such as the Committee for Veterinary Medicinal Products (CVMP) within DG III (Internal Market and Industrial Affairs). Feed additives are reviewed by the Scientific Committee for Animal Nutrition (SCAN) of DG VI (Agriculture). The external expert committee reviews the product application and when all questions and concerns about the product and its manufacture have been satisfied, reports their findings back to the Commission which gives final approval. As we found out with the anabolic hormones, the Commission does not have to accept the findings of the scientific committee. In addition, requirements of the approval are not binding on the member states; e.g., they can set different requirements, such as withdrawal time. Products can also be approved and marketed in a member country without (or before) receiving full EC approval. There are currently three "hurdles" that a product must clear to receive EC approval. They are Safety, Efficacy and Quality. A fourth hurdle has been proposed (and recently withdrawn) which would require a Socio-Economic Impact Assessment. However, it could be reintroduced in the future.

Canadian Regulatory Authorities

New animal drug approvals in Canada are regulated by the Bureau of Veterinary Drugs (BVD), which is in the Ministry of National Health and Welfare. It operates similar to the U.S. FDA in that its staff of reviewers makes internal scientific decisions on product submissions. The BVD also issues experiment test permits for efficacy trials called Investigational New Drug (IND) permits. Following approval, some of the regulatory responsibility shifts to Agriculture Canada which monitors residue levels in food similar to the USDA responsibilities.

Animal Health Product Development

Now let us turn in detail to the development process and discuss the requirements that a product must meet enroute to approval. Depending on the product, these steps may change slightly in order because each type of product category has its own regulatory concerns. Since this is an animal growth and development session, we will concentrate on the development and approval process for a food animal production drug, one which might have a label claim for increased rate of weight gain and improved feed efficiency. Many of you are probably familiar from your research with at least one of these drugs. To the general public and within the FDA, the major concerns for production drugs center on residues and human food safety. This is due to their being administered to many animals (mainly food animals) over a long period of time, in many cases up to marketing. Additional concerns center on efficacy, target animal safety and environmental impact. We will concentrate our discussion on the efficacy and safety sections of the development program.

Discovery Program for New Animal Drugs

The Discovery section is the foundation of our research programs and provides us with potential new products. All companies have what we call screening programs, these are in-vivo or in-vitro test systems where we evaluate the specific activity of many compounds on a continuous basis. These systems are models for a particular disease or metabolic event. These systems should be capable of screening thousands of different compounds per year. Except for chick battery screens, no screening that I know of is conducted in the target animal. It is far too expensive, slow, laborious and requires huge quantities of compound and destruction of many animals. Most compounds screened are available only in milligram amounts. The use of in-vitro tests is becoming commonplace for screening.

The next step after confirming the results through retesting is to go to in-vivo (usually rodent) models that mimic the desired event of the target animal. These tests also allow for the collection of initial data on the toxicity and pharmacology of the new compound. These are closely followed by initial preclinical trials in the target animals. These are designed to confirm the desired activity, estimate the probable effective dosage, determine the best route of administration and potential formulations.

During the advanced stages of discovery, many other activities are taking place in the company. Process chemists are determining how to produce large quantities of the compound and predicting what it may cost to manufacture. Analytical chemists are developing methods to identify the specific molecule in feed and tissues. Residue and formulation staff are getting their first experience with the compound.

In the Discovery stage, there are three key questions that need to be answered. 1) Has the compound's potential activity been confirmed in the target animal? 2) Does the compound have undesirable side effects which might indicate future toxicological problems? Is it highly toxic? Is it a potential cancer-causing agent or is it mutagenic in any way? 3) Based on probable dose level, length of treatment period and cost of manufacturing, will the compound be cost-effective to develop and market? If the answers are correct, then the compound is a candidate to enter the product development stage.

Product Development to Meet Regulatory Requirements

Entering development with a compound means that the

company has made a major commitment of both time and money to the future of the product. Most of the work conducted in development is designed to provide the data required by government regulatory agencies and the data necessary for the company to decide if the product should be brought to the marketplace.

Efficacy Trials

Entering the efficacy phase of this program, the company will be conducting sufficient preclinical trials to conclude what the probable use level (or range) is, that the product is safe to the target animals and that it has market potential. In addition, initial human food safety and residue studies should have shown no concerns. The next step is to notify the FDA that a new compound is under investigation. The sponsor company submits to the FDA a "Notice of Claimed Investigational Exemption for a New Animal Drug" which establishes an Investigational New Animal Drug (INAD) application. The FDA will assign an INAD file number to the product, which allows the company to ship limited quantities of product to outside investigators for trial purposes. The FDA must be informed in detail about each drug shipment at the time of shipment. If sufficient residue, metabolism and human food safety data are available, the sponsor company can apply for a INAD marketing permit which, if approved, will allow for a limited number of treated animals to be sold for human food provided strict conditions of animal treatment, drug withdrawal, slaughter notification and inspection have been followed. These marketing permits are not easily attained and the conditions must be followed to the letter. They do allow the companies and investigators to recoup some of the costs of conducting the research as well as preventing the destruction of thousands of test animals.

Information supplied with the INAD application may include: 1) identity of the new animal drug; 2) investigational labeling to be used on the material; 3) name and address of proposed investigators; 4) number of animals to be treated and amount of drug shipped; 5) a commitment that edible products from treated animals will not be used for food without prior FDA authorization; 6) approximate date of beginning and end of proposed trials; 8) name and location of slaughter facility where animals will be processed; 9) data to show that edible products from animals treated with the maximum dose for the maximum time period do not contain harmful residues and 10) results of preliminary efficacy, safety and toxicity studies. FDA comments on study protocols for the required clinical dose titration trials can also be requested at this time.

The actual clinical field trials are designed to demonstrate a product's safety and efficacy. The studies include dose titration, dose confirmation and target animal safety trials in target animals raised under conditions simulating commercial practices. Sufficient test animals and replicates are used so that the results can be statistically analyzed and the response validated. Efficacy studies must be conducted in at least three different geographic locations. All investigators must be qualified by scientific training and experience to evaluate the safety and/or effectiveness of the experimental drug. The researcher is also required to retain complete records of the investigation, including records of the receipt and disposition of the experimental material for two years.

The trial site and records are also open for potential inspection by the FDA at any time during that period. The FDA has issued a specific Preclearance Guideline for Production Drugs — Efficacy and Safety Guidelines to provide sponsors with information for conducting these trials. The protocols for the pivotal trials, those which the FDA will use to determine the use level and product label claims, must be agreed upon with the FDA before the studies are conducted. The target animal safety trials must be conducted under Good Laboratory Practice (GLP) procedures.

The following list will provide you with an example of what information is considered during development of the pivotal dose titration trial protocol: 1) label claims (e.g., for increased rate of weight gain and improved feed efficiency) to be evaluated; 2) dose levels to be used, which must include at least three non-zero levels plus controls and assay program to verify dose levels used; 3) target animal species and class; 4) market areas to meet three (minimum) geographic locations requirement; 5) ration formulations - must use common feedstuffs from the geographic area and diet must meet or exceed National Research Council recommendations, fortified diets may have to be used with certain production drugs, requiring additional conventional controls be run; 6) duration of treatment - should be for an entire production period (e.g., finishing period from 55 kg to slaughterweight); 7) management practices - feeding, water, space, penning, etc. - should simulate commercial practices; 8) animals to be used - breeds, sexes, weights, etc.; 9) concomitant drug use - it is strictly forbidden to use any other drugs during the experimental period even if such use is common commercially (e.g., do not use antibiotic feed additives during an implant growth promoter trial) and 10) supplemental data being collected (e.g., carcass data).

Results from these trials will be used by the FDA to set the approved use level for each individual label claim evaluated. The use level is defined as the effective range and is determined statistically, using linear plateau and polynomial regression models.

Trial Monitoring Responsibilities

It is the responsibility of the sponsor to monitor each study before the trial begins, periodically during the trial and after the trial to collect the data and investigator's report. This is a time-consuming and expensive job and must be done on all target animal clinical trials conducted under the INAD. The required drug shipment notice informs the FDA of the trial, investigator, location, number of animals and experimental design. A drug inventory system to log in drug received, drug used and drug returned to sponsor must be set up for each investigator. Standard Operating Procedures (SOP) must also be established for all routine operations conducted during the study.

Due to these requirements, it is becoming more and more difficult for companies to justify sending out experimental samples of new animal drugs to investigators such as many of you in the audience. Companies receive numerous requests for samples of new animal drugs for experimental use but, because of the regulatory responsibilities, most of these requests can not be honored. Regulations for experimental

samples for use in in-vitro tests or in laboratory research animals are not as strict but nevertheless require that records of each drug shipment be kept and made available for FDA inspection. As part of this monitoring, it is our responsibility to inform the FDA of any finding associated with the use of the new animal drug that indicates that it is not safe for the intended use. Use of the drug in food-producing animals not covered under the INAD is strictly forbidden. The sponsor company is also not allowed to distribute or test-market a new animal drug until it is approved. Finally, it is required that all data from each and every target animal study conducted with the new animal drug be submitted to the FDA as part of the New Animal Drug Application (NADA) dossier. This application is submitted when a company believes that all the FDA requirements have been met and the company is ready to manufacture and distribute the product commercially.

Target Animal Safety

Studies must be conducted by the sponsor company to assure that the new animal drug is safe for the intended use and to identify signs of adverse or toxic effects for product label warnings. This requirement is met by conducting studies in the target animal under essentially the efficacy protocol conditions with the added need to examine elevated dose levels (up to 25 times use level) over an extended treatment period. Signs of adverse effects and product toxicity must be documented. Gross pathology and histopathology on all organs and tissues is required on select animals during the study or on any animal that dies during the study. Reproduction studies may also be required, depending on target animal and product pharmacology. All safety-related studies must be conducted under GLP procedures.

Human Food Safety

Food Animal Residues

If the new animal drug is to be used in food-producing animals, a series of tissue residue studies must be conducted. These studies show whether and where the compound and/or metabolites will accumulate in the edible tissues and how rapidly the residue will be eliminated from the tissue and animal. Most of these studies are conducted with radiolabelled compounds. Parallel metabolism studies in rodent models may also be required to further examine the metabolism of the compound and the major metabolites formed. If the rodent model handles the drug similar to the target animal, then this will reduce the requirement for toxicity studies with the major metabolites due to what is called autoexposure. The sponsor must also develop precise chemical analytical methods for use in drug residues studies. Additional regulatory and confirmatory methods must be developed for use by the government for monitoring of residues in food. The method needs to be confirmed by FDA and independent laboratories and is then kept on public file at FDA Headquarters. This "cold" assay is used in detailed residue studies designed to allow the FDA to calculate a drug withdrawal period and, if appropriate, a residue tolerance level for the drug. The residue depletion and tolerance levels also must be confirmed under field conditions. As with other safety studies, the residue work must be conducted under GLP procedures.

Toxicology Studies to Examine Human Food Safety

These are critical studies for animal health products intended for food-producing animals. Toxicity must be evaluated on the parent compound and on any major (>10% of parent compound) metabolites that either are not tested through autoexposure (rodent does not form this particular metabolite) or if they have the potential to be more potent or toxic than the parent compound. The compounds tested must comprise at least 90% of the residue material in tissues. These studies are intended to examine two main issues: safety of drug residues and safety to anyone handling the drug from manufacturing to end-user. The purpose is to define the biological effect(s) of the compound and to determine its quantitative limits so that an Acceptable Daily Intake (ADI) can be calculated by the FDA. This ADI will include a margin of safety (usually 100X to 1000X) depending on the study used in determining the value. Each individual toxicity study must be conducted with appropriate dose levels that will allow a determination of a dose that produces an adverse biological effect in the test animals and a dose that does not produce any significant toxicological or pharmacological effect. The latter is called the No-Adverse-Effect-Level or NOAEL. The NOEAL from the most sensitive test (i.e., lowest dose, in mg per kg body weight, required to produce an adverse effect) is then used in calculating the ADI. The ADI is in turn used to calculate the residue tolerance level and the withdrawal period, using statistical procedures. The sponsor works with the FDA to determine the necessary studies based on proposed drug use, probable human exposure to parent compound and/or metabolites, possible biological effects based on structure-activity relationships and on any observed effects in initial biological studies. The FDA and sponsor company must also agree on the protocols for each study. Human food safety is usually the most time-consuming and expensive part of the development. There are few shortcuts available and none for a new chemical unrelated to any previously approved by the FDA. All toxicity tests must be conducted under GLP procedures.

Required Toxicology Studies

Compounds closely related to existing compounds may need only abbreviated or targeted toxicology studies, although certain acute and chronic studies are required for all compounds. As a preliminary step in the evaluation of human food safety, a new compound will first undergo a select series of genetic toxicology studies to determine if it is a potential carcinogen. This is usually initiated and done prior to establishing the INAD. With the current emphasis on food and employee safety, any confirmed suspect carcinogens are immediately dropped from further consideration. Companies do this not only because of potential regulatory difficulties but because many of their employees will be exposed to the compound in the laboratories, feed mills and in animal testing. A full battery of genetic toxicology tests are conducted during the development program. These results will be used later to determine if chronic (2-year) oncogenicity studies are necessary. Ninety-day rodent (usually rat) and non-rodent mammalian (dog) are required on all compounds. To examine effects of the compound on reproduction, a study is

conducted in male and female rats which are continously fed the compound through two generations. This test also examines teratology aspects of the compound during the in-utero period. To examine teratology further, developmental toxicology studies are conducted in both rats and rabbits.

Additional Toxicology Studies

Depending on the nature of the compound(s) and the findings in the initial tests, the sponsor and FDA determine if additional toxicology studies are necessary. In almost all cases, a new compound must undergo chronic (2-year) bioassays in two rodent species to evaluate its carcinogenic potential. The requirement for this is based on the FDA's Threshold Assessment of potential for carcinogenicity. This is a Category Assignment based on structure, genetic toxicity, subchronic (90-day) studies, etc. that are used to assess carcinogenic potential. An additional chronic feeding study in a non-rodent species may also be requested. Depending on the biological activity of a compound, additional studies may be asked for in the areas of immunotoxicity, neurotoxicity, hormonal activity and for toxicity of the biomass of fermentation products. Selecting the correct dose levels for chronic studies in laboratory species is a science in itself and requires considerable experience and skill.

Further Requirements

In addition to the above regulatory areas, there are several other important sections in a submission. Examples would include product stability, formulation specifications, manufacturing processes, manufacturing facility, examples of product labels and package inserts, environment impact and the Freedom of Information summary. The latter two sections are on public display and copies can be obtained under the Freedom of Information Act.

The efficacy and especially the safety and toxicology data which support the registration are usually not published prior to FDA review. However, supporting study data not critical for FDA review is often published. By law, the material submitted for registration is kept confidential by the FDA prior to approval. The official notice of approval is published in the Federal Register.

References

Animal Health Letter. 1990. Animal health product development and approval. Animal Health Institute, Alexandria, VA. January-March 1990.

Code of Federal Regulations. 1990. Title 21:500-599. U.S. Government Printing Office, Washington, D.C.

Knight, W.M. 1987. Responsibilities of animal scientists and drug sponsors when conducting research with investigational new animal drugs. J. Anim. Sci. 65:581-583.

Parrott, J.C. 1987. Responsibilities of university investigators when conducting trials on investigational new animal drugs. J. Anim. Sci. 65:577-580.