Animal Drug Development and Consumer Protection: An Historical Review

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I am flattered to be invited to participate in this, the jubilee celebration of the federal agency that is concerned chiefly with the safety of food and drugs so essential for human life. However, I have a dilemma. It reminds me of the story told of the late Supreme Court Justice, Oliver Wendell Holmes, who once found himself on a train, but could not locate his ticket. While the conductor watched, smiling, the 88-year-old justice searched through all his pockets without finding the ticket. The conductor, of course, recognized the distinguished passenger. So he said: Mr. Holmes, don't worry. You don't need your ticket at this time. You will undoubtedly find it when you get off the train and I'm sure the railroad will trust you to mail it in due time. The justice looked up at the conductor with some irritation and said "My dear man, that's not the problem at all. The problem is not where the ticket is, the problem is where am I going?"

My problem is what this distinguished audience expects me to say in the time allotted to me. Much has transpired in the past 75 years regarding the areas in which the federal agencies, especially the FDA and United States Department of Argiculture have interests and responsibilities as well as the industries that are regulated by these government agencies.

The identity of the FDA begins with the word "food". Agriculture, the chief source of food, is the most basic enterprise in the United States and, of course, that also applies to most other countries. It has been said that a famine has never been experienced in any country that has had and maintained a thrifty livestock industry.

Animal agriculture in this country has become fairly sophisticated in the past fifty years and utilizes modern scientific techniques. This aids in the production of food, especially of animal origin, and is more economically produced in the United States than in any other country in the world. As a result, food is available at a lower cost to the consumer. An example of this is the U.S. poultry industry, which employs scientific methods with respect to housing, breeding, feeding and disease control, and is producing poultry meat and eggs in greater amount and at a lower cost than any other place in the world.

In addition, U.S. transportation and refrigeration procedures provide foodstuffs, especially those of animal origin (i.e., fresh frozen and processed meat; milk, cheese and other dairy products; poultry meat and eggs: manufactured foods that include the above) to the consumer in excellent condition and in shorter periods of time from production to market than in most countries.

This has not always been the case. As an example, in 1900 one farmer produced enough food for 7 people, in 1950 for 16 people and in 1980 for 60 people.

A recent report from the National Academy of Agriculture indicates that 25% of our work force generates some 20% of the U.S. Gross National Product, yet the actual production of food involves only about 3% of the American labor force.*

As a part of the American population moved from the rural areas to the industrial centers in the late 1800's and early 1900's, food was transported rather slowly by horse-drawn vehicles or the then available railroads. Only primitive procedures for preserving as well as the transportation of foodstuffs were then available.

In the early days of industrial development in this country, much of the fluid milk (so-called fresh milk) was produced near metropolitan areas where there was the greatest demand. The dairy farms frequently were located in the neighborhoods where breweries were operating. This was so because wet distiller's grains (wet mash) was an important item in the cattle ration. However, sanitation procedures were more or less non-existent by today's standards. This often resulted in greatly contaminated milk. Pasteurization was not yet extensively used, and adulteration with chemicals (i.e., Formalin) to preserve the product was practiced by some operators. In addition, some unscrupulous dealers diluted milk with water.

Milk produced in distant rural areas was generally separated on the farm and the sour cream was used in the manufacture of butter. Such cream frequently was poorly refrigerated and shipped to butter manufacturing plants, often located at distant places.

**John Witter: American Agriculture: Research to Meet Human Needs in the 21st Century, Westview Press, Boulder Colo. 1980, p.331.*

It has been reported that at times it was necessary to wire the lids on the cream cans to prevent them from being blown off by the fermentation process. Sometimes, sodium bicarbonate was added to control the process.

An acquaintance of mine had an extensive business, selling and distributing hand-operated cream separators to dairy farmers in Wisconsin, in the early 1900's, and in later years this same enterprising Scotsman became interested in buying fresh whole milk from farmers in the same Wisconsin area and separated it in very modern milk plants, selling the cream to eastern markets or manufactured sweet cream butter.

The publication of the well-known book, The Jungle, which refers to the meat packing industry of the early 1900's, by Upton Sinclair, undoubtedly motivated individuals to give serious action to correct and/or eliminate some of the potential human health hazards, related to food and especially meat and meat products.

As we reflect on the history of the development of a federal control program for food and drugs, we must give credit to Dr. Harvey W. Wiley, Chief of the Bureau of Chemistry in the United States Department of Agriculture, who recognized some of the hazards in the production and distribution of food as well as chemicals that were available at that time. In fact, he conducted what we would call today a clinical safety or toxicity study in human volunteers. This was carried out with a group of young men who were fed measured amounts of food preservatives, such as boric acid and salicylates, which were commonly added to human food.

Happily, in the early 1900's, some individuals interested and engaged in the chemical, pharmaceutical and meat industries, recognized the seriousness of these problems and took it upon themselves to cooperate with Dr. Wiley and his colleagues in drafting and encouraging federal legislation to insure the quality of their products and to protect the consuming public. This cooperative effort resulted in the introduction of federal statutes to provide some control of foodstuffs and drugs from a safety point of view. The original United States **Pure Food and Drug Act** and the **Meat Inspection Act** both were enacted by the Congress and finally signed on June 30, 1906 by President Theodore Roosevelt. It is in this connection that we are celebrating this diamond jubilee. The Meat Inspection Act provides supervision of the wholesale meat processing activity and the Food and Drug Act has responsibility of the final form of foodstuffs, as well as drugs, cosmetics, biologics (human) and devices.

The legislation provided regulations to prohibit the interstate commerce of misbranded and adulterated foods and drugs. Incidentally, administration of the established regulations of the Pure Food and Drug Act at that time was headed by Dr. Wiley.

Many amendments to the original act have been made during the past 75 years, and I will only mention a few that have a significant effect on animal drug development.

Much progress was made in succeeding years, especially with the cooperation of conscientious members of the chemical, pharmaceutical, livestock, and meat and milk industries.

It was not until 1938 when further significant legislation was enacted. This was identified as the **Federal Food, Drug and Cosmetic Act (FDA)** and contained provisions for the evaluation of new drugs and other desirable standards for drug manufacturing. The 1938 action followed the 1937 episode of poisoning in more than 100 persons who had been treated with an elixir of sulfanilamide which had not been adequately tested for potential toxicity.

Needless to say, this development was long overdue and provided some control of drug products from a safety point of view. The 1938 act and subsequent regulations have greatly increased the spectrum of responsibility and authority of the Food and Drug Administration.

The 1958 amendment to the act prohibits the use of direct or indirect food additives until the sponsor establishes safety and then the agency issues regulations which specify conditions of use. This authority extends to the use of chemicals in food producing animals because milk, meat and eggs, or products of the same, may contain significant and possibly toxic residues.

The administration of this amendment resulted in the procedure of drafting and issuing regulations describing in detail how chemicals and drugs are to be used in food producing animals. Prior to the 1958 amendment chemicals used in livestock received rather limited attention by the FDA. In 1927 one veterinarian was employed and his duties were to evaluate and screen vitamins and minerals as they might relate to nutritional requirements in animal rations as well as claims that were made for the same. That person also evaluated medicaments for their use and safety in animals if the preparations were brought to his attention.

It is recalled that in the early 1940's a sulfonamide compound had been studied extensively from the standpoint of safety and efficacy in several species of animals. The data collected in those studies were submitted, including suggested dosages and indications as a new animal drug application for the use of the compound in domestic animals.

The new drug application was reviewed and approval was granted ten days after receipt of the application. I dare say this was the shortest period of time for the review and subsequent approval of a new chemical entity for animal use with which I am familiar. This compound has been used satisfactorily in animals for many years.

The regulations to administer the 1958 amendment to the act greatly increased the responsibility of the agency. To properly deal with these problems, additional personnel were required including chemists, toxicologists, physicians, animal scientists and veterinarians as well as administrators in order to carry out the review of submitted data and prepare and publish specific regulations for the use of the direct and/or indirect food additives.

In 1965 the FDA reorganized the agency and created the Bureau of Foods and the Bureau of Veterinary Medicine to deal with drugs and chemicals designed for use in food producing animals. This is evidence of the importance of animal drug development and use.

Some of the indirect additives include those that may be retained in food of animal origin. Thus it is necessary that meaningful assay procedures be available for surveillance purposes. Information regarding the fate of compounds given to food producing animals is necessary and especially to determine the duration of time in which residues in tissues (milk, meat and eggs) would be in excess of allowable tolerances.

The arbitrary human safety factor for potential drug residues in food must be greater than 2000. The maximum residue limit is determined on the basis of no effect level shown by 90 day toxicity studies in two unrelated species of laboratory animals. In many countries, the so-called safety factor is much lower and possibly accounts for some compounds being available there and not in the United States. With some compounds, very specific analytical and more extensive toxicity studies allow the establishment of tolerances for low levels in food stuffs.

If concentrations greater than the allowed tolerance or concentrations are found, it is concluded that there is violation of the adopted regulations and thus adulteration of the food of animal origin.

During the 1950's, chemicals and fermentation products were found that could be used beneficially in livestock production and that could be given in the feed for herd and/or flock administration. In order to ensure the success of this procedure it is natural that proper mixing techniques be developed and that careful assays be conducted on the finished feed offered to the animals. This then extended the regulatory activities of the FDA to the feed manufacturers and compounders. Needless to say, this had necessitated considerable work from a standpoint of technology and improving testing methods to determine stability of the product as well as studies to determine the safety and efficacy as well as acceptability for livestock.

It also has greatly increased the work of the control agency in providing surveillance of the feed industry that is involved in preparing medicated animal feeds. It might be said that feed manufacturers are preparing dosage forms for mass medication of lifestock and poultry.

In addition to the activities of the FDA, the Food Safety and Quality Service of the U.S. Department of Agriculture has the responsibility of supervising the production of wholesome food and especially of animal origin. Thus the agency must provide surveillance of these food items for chemical content in accordance with FDA regulations.

Further legislation that had a significant impact on the development of new drugs for use in humans and animals were the **Kefauver-Harris Amendments** of 1962. The regulations for the administration of these amendments require drug manufacturers to provide convincing evidence of effectiveness of their products as a condition for marketing approval.

In 1966, the FDA contracted with the National Academy of Science/National Research Council to evaluate the effectiveness of many thousands of drug preparations that had been approved on safety alone between 1938 and 1962, but not necessarily for efficacy in the clinical use. This has eliminated many products designed for use in humans and/or animals. It also has introduced the need for much additional work, and expense, for manufacturers to satisfy the agency's requirements. Industrial funds for this defensive research and testing have had a tendency to reduce the investment for basic research for new and better drugs. In addition, science has advanced and other new requirements must be met, thus some worthwhile preparations used for long periods of time are no longer available. These more recent so-called advances have cost the pharmaceutical industry large amounts of money, and as a result, very cautious steps are taken these days in the search for new drugs. This is especially true for livestock products because of the economics involved. Animals (food producing or companion) usually have a definite economic value (dollars and cents) or market value and there is a limit to the amount of money an owner will invest in preventing or treating disease in animals in his possession.

The problems in this connection may very well have some adverse effect on food production of animal origin unless the agency adopts a less stringent interpretation of some of the regulations currently under consideration.

The 1968 amendment to the act brought together regulations regarding new animal drugs which previously were defined and administered in several areas of the control agencies. This has aided greatly in dealing with the problems in animal drug development.

Much credit is given and/or taken by the regulatory agencies for the improvement of human health because of the activities of the FDA. However, we must not lose sight of the fact that the well-being and health status of our citizens have also been benefited from other practices and procedures. The following have made significant contributions in this regard: improved housing and water supplies, vaccination programs with effective biologic products, elimination and/or control of some zoonotic diseases, modern refrigeration, rapid transportation, improved packaging materials, pasteurization of milk, education including school programs, radio and television communication among the citizens of the country. All these have contributed toward a higher health standard for the American public.

Following is a brief list of diseases of **humans** which at one time were prevalent in this country and today appear to be under control and/or practically eliminated: scarlet fever, typhoid fever, tuberculosis, (lymphoid and bone) small pox, diphtheria, measles, pneumonia and poliomyelitis.

Animal disease also has been greatly reduced or

eliminated: tuberculosis, brucellosis, rabies, parasitism, Marek's disease and pullorum disease in poultry, hog cholera, histomoniasis (blackhead) in turkey, canine distemper and hepatitis, feline infectious enteritis, some enteric conditions, and several nutritional deficiencies in livestock.

Indeed the current health delivery system, as well as food distribution practices, with all the faults, is a great improvement over what was available when the original Pure Food and Drug Act and the Meat Inspection Act became effective. Medical practice and veterinary practice have changed, and I might add dramatically, in our lifetime. The identity of specific antimicrobial agents, anesthetic and ataractic drugs, anthelmintic agents, coccidiostats, to name a few, have certainly contributed significantly to these practices. **It should be stated all of these agents have received close scrutiny by the FDA and explains the increase in the budget and manpower of the agency in the past three decades.**

The livestock and poultry industries have in the past thirty to forty years undergone drastic changes. Intensive production systems have been introduced in many areas and especially as far as swine, cattle and poultry. This includes management, feeds and feeding as well as disease control methods. Flock and herd treatment procedures have been developed and found practical. Extensive nutritional studies have been conducted and the results of these are applied. In addition, effective disease prevention methods too have been developed, an example being the control of coccidiosis in chickens where low levels of drugs in the feed are provided on a continuous basis for young chickens. The principle of flock and/or herd treatment with chemicals is now an accepted and useful procedure.

In addition, chemical compounds and fermentation substances likewise are used extensively in both poultry, cattle and swine as growth promotants and to improve feed efficiency. This actually saves livestock feed and is reflected in the cost of food of animal origin.

In the late 1970's considerable controversy developed regarding the use of antimicrobial agents in livestock production and especially the subtherapeutic use of antibiotic substances, primarily penicillin and tetracyclines. This stimulated the Congress of the United States to provide an appropriation to evaluate potential ill effects on human health when these substances are used in animal feeds and requested the FDA to withhold further action pending completion and consideration of a study by the National Academy of Sciences.

The National Academy of Sciences/National Research Council was given the task to conduct a careful review of the available information. An appropriate committee was selected to pursue the assignment and the members consulted many knowledgeable individuals regarding the subject.

In 1980 they issued a report as a result of an extensive study and "concluded that the postulated hazards to human health from subtherapeutic use of antimicrobials in animal feeds were neither proven nor disproven." "It also was indicated that the research necessary to establish and measure a definite risk has not been conducted." Thus the controversy continues and the outcome is unknown at this time.

Considerable scientific progress has been made in recent years regarding the detection and identification of chemical substances and metabolites including finite amounts in tissues of animals treated with such substances.

Positive evidence of violative concentrations have been found, especially in meat without clear evidence of toxicity in animals, or humans that may have consumed such meat. This has presented the control agencies (PDA and USDA) as well as the livestock industries with additional problems and at this time there is uncertainty as to what the effects will be on the industries.

During recent years a good deal of concern has developed regarding the potential hazardous effect on human health of antibiotics, toxins, chemical and possibly microbial contaminants in processed foods of animal origins. Monitoring and testing systems are available for some but not for all possible contaminants and residues. There is no formal system currently available for monitoring all inadvertent contaminent in animal feeds and/or the environment.

However, emergency quality assessment programs for chemicals, mycotoxins and heavy metals are being developed jointly by the food and drug administration, department of agriculture and the environmental protection agency which we trust will prevent serious consequences among our human and/or animal populations.

Examples can be cited where animals and, in some cases, large numbers were poisoned by ingesting unrecognized chemical contaminants in feed.** Carcasses from such animals usually find their way to rendering plants, where hides and sometimes meat is salvaged and processed as animal by-products which are fed to livestock, and in this manner residues may enter the food chain as indirect additives. In view of this possibility, the FDA and especially the Bureau of Veterinary Medicine as well as USDA have responsibility to prevent, if possible, the adulteration of human food through such practices. Needless to say, this calls for rapid and careful investigation of such incidences. **In many cases the attending veterinarian is the key person in dealing with the problem of poisoning in livestock.**

(Ref. "The Effects on Human Health of Subtherapeutic Use of Antimicrobials in Animal Feeds" by the National Academy of Sciences. Washington, D.C., 1980).

***William B. Bixler, VDM-Feed Industry "Spotlight", Fourth Quarter 1980/*

***Jane F. Robens, DMV-Proceedings of 84th Annual Meeting of the U.S.A.H.A., November 1980.*

Needless to say, controversies arise from time to time in the development of substances for use in man or animals, with today's requirements based on current and possibly future regulations between the regulatory agencies, the animal, chemical and pharmaceutical industries and indeed the public (i.e., consumer organizations). For a number of years various groups have suggested that in such cases peer reviews be provided and this may very well occur in the future.

One well-known congressman, Representative William C. Wampler from Virginia, has proposed legislation to establish a National Science Council. Such a body would include scientists to explore and arbitrate issues of food safety if there is controversy between the sponsor and the regulatory agency. Several scientific organizations also have expressed interest in participating in such service to our public health practices. It is my understanding that this idea is already in effect in a sense that several issues are being considered in what some have chosen to call a science court.

It would appear that an increasing number of individuals are of the opinion that scientific talent outside of the regulatory agencies could and should be utilized. In this connection, the idea of risk assessment would undoubtedly be considered and this certainly would be of interest to the livestock industries.

It is encouraging to see that the FDA has extended the so-called "fast track" review program for much needed animal drugs. This will help the animal industry in the future as animal drugs are being developed on an international basis.

In the past few years there have been increasing demands by the FDA for information and test methods which have been very expensive to develop and provide, for substances intended for use in food producing animals. However more recently, there has been some indication that the FDA might consider a so-called "softening of its regulatory demands". Thus one might be encouraged by the often quoted comment by Dr. Lester Crawford, former director of the BVM, in a message to Dr. Jere Goyan, then commissioner of FDA. *"Cyclic review and the sensitivity of method for testing for chemicals (SOM)*** may well imperil new animal drug research, dangerously shrink the veterinary medical armamentarium and escalate livestock production costs."* He concluded that these policies *"might prove to be well-intentioned public health imperatives that cannot be practically afforded"*. (from M.V.P. March 1981).

Many persons involved in the industries appreciate these statements and trust that subsequent administrators will give equal consideration to them.

This, then, is a brief summary of the 75 years of activities of the Food and Drug Administration as well as items of interest to the Animal Health Institute with respect to animal drug development and consumer protection.

****Proposed regulation "Compounds used in food producing animal: Procedures for determining acceptability of assay methods used for assuring the absence of residues in edible products of such animals".*

For Your Library — Food Animal Surgery

J. L. Noordsy, *D.V.M.*
Published by Veterinary Medicine Publishing Co., 144 N. Nettleton, Bonner Springs, Ks. 66012.

Price: $22.50
Spiral-bound, 8½" x 11", drawings, 181 pp.

Dr. Noordsy reminds us in the introduction to his new book that **time is trauma** when surgery is performed on food-animal species. Dr. Noordsy must also believe that this axiom holds true for readers of his new book, because he presents his outline of surgical procedures in a direct, concise, and easy-to-follow format.

The book is in outline form and is based on notes from Dr. Noordsy's courses in food-animal surgery at Kansas State University. It does not resemble a textbook, however, and could better be described as a field manual of surgical techniques.

Methods of physical restraint, anesthetic techniques, and the common nerve blocks are presented in the first section. The second section contains 24 chapters, each describing indications and step-by-step procedures for the most common food-animal surgical procedures. Review questions are at the end of each chapter.

Often several techniques for treating the same condition are presented in conjunction with comparative indications for each. For example, seven techniques are presented for correcting a bovine vaginal prolapse. This presentation of several techniques will allow practitioners to apply some new methods to old problems.

This book is an excellent reference for any food-animal clinician.