General Session

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The Bureau of Veterinary Medicine and the Bovine Practitioner

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Regulatory control over new animal drugs and medicated feeds originated in 1938, under the new drug provisions of the Federal Food, Drug and Cosmetic Act. These provisions enabled FDA to prevent the marketing of both new animal drugs and medicated feeds until their safety had been demonstrated. In 1962, the Act was amended to require demonstration also of the effectiveness of the drugs and the medicated feeds containing them.

In 1968, Congress enacted the animal drug amendments which created a section of law dealing exclusively with animal drugs and medicated feeds. Prior to these amendments, which became effective in 1969, animal feed drugs were regulated as new drugs and food additives; the latter under the Food Additives Amendment of 1958. The 1968 amendments retained all of the new drug requirements of the 1938 law, as amended in 1962, requiring adequate proof of safety and effectiveness of new drugs before their marketing.

Under the 1968 amendments, a new animal drug is deemed to be unsafe with respect to any particular use or intended use, and therefore, adulterated if the drug is not covered by an approved new animal drug application (NADA).

If such a new unapproved animal drug is used to produce a medicated animal feed, the feed is also deemed to be an adulterated drug. The Federal Food, Drug and Cosmetic Act prohibits the interstate shipment of such adulterated drugs or their use in the manufacture of other animal feeds.

If you were a lawyer, you would have immensely enjoyed those opening remarks and the vast implications entailed thereof. But being a bovine practitioner, it probably means little to you. Because of the increasing importance and impact that FDA has and will have on food animal production, I believe it is imperative that you have a better understanding of the provisions of the FD&C Act and associated regulations as regards your role as a bovine practitioner. Thus, my discussion this morning has two objectives:

1. To present the role of the Bureau of Veterinary Medicine (BVM) in regulating food animal drugs, principally in the bovine, a species in which you are most interested.
2. Delineate the role that research plays in this procedure, which is a function with which I am most familiar.

Viewgraph 1

The drug manufacturer spends several years in the development of data to support his request for approval of a new animal drug application. In the developmental stages, oftentimes he has filed with BVM, and Investigational New Animal Drug application (INAD). The INAD is simply a document containing preliminary information on the toxicity of the compound, and contains preliminary data on the excretion rate of the drug from body tissues. The data must be sufficient for BVM to make a determination that this drug can be safely tested under limited and specified restrictions in either controlled laboratory or field conditions. In due time, the data is sufficient for the sponsor to prepare and submit a NADA. The BVM then initiates a pre-market review and evaluation of this data.

There are three major highlights to the review of a NADA. These are:

1. Analytical methodology (drug residues and safety to man).
2. Safety to the animal.
3. Efficacy of the drug.

I. Analytical Methodology:

a. Development of adequate chemical or biological methods by which to detect residues of drugs in

tissues of treated animals is frequently the most time-consuming and expensive item in the development of a new animal drug for use in food-producing animals.

b. Development of residue methodology for a drug is interrelated with toxicological studies to establish its safety. For example:
   1. If residue methodology is of sufficient sensitivity to detect residues at 0.1 ppm in muscle, liver, kidney and fat, and if these levels are achieved after a practical withdrawal period, the drug may be granted a negligible tolerance, *provided* that 90 day subacute toxicity studies in two species of mammal established a 2000-fold margin of safety between the highest level fed with no effect and the proposed negligible tolerance.
   2. If the residue methodology is not adequate to detect residues at 0.1 ppm or the withdrawal time required to achieve this level is impractical, a finite tolerance must be established. A finite tolerance must be supported by two-year chronic toxicity studies in two species of mammal. Data must establish at least a 100-fold margin of safety between the highest level fed with no effect and the proposed tolerance.
   3. Tolerances for milk and eggs must also be supported by multi-generation reproductive studies.
   4. If metabolites occur at significant levels, studies must be performed to establish that they are no more toxic than the parent compound.

If the subject chemical is a suspect or confirmed carcinogen, then the Delaney Clause of the Food Drug and Cosmetic Act becomes applicable. This is a very complicated and controversial area which could stimulate a two- or three-hour discussion; therefore, we will bypass it for now and simply say that the Delaney Clause means there will be "no residue" detectable by the most sensitive method currently approved by FDA. A great deal of research and effort is being devoted to clarifying the full intent and interpretation of the Delaney Clause.

II. Animal Drug Safety: A few considerations are as follows:

a. Potential or acute side effects, adverse reactions, individual idiosyncrasies, sensitivities, anaphylactoid reactions and potentiations.
b. One must consider whether age, sex, breed, species, lactation or pregnancy or other such parameters alter the effect of the drug.
c. One must consider the effects of method and/or duration of administration, adjunctive therapy, management practices and stress.
d. One must consider the possibility of delayed responses.
e. The margin of safety for the drug must be established. Many drugs which have a narrow spectrum of safety (2x or less) may require much more restrictive usage patterns.
f. Depending of the method of administration, irritation or hemolysis testing may be necessary.

III. Animal Drug Efficacy: This is an area where bovine practitioners are often called upon to assist in the development of data. There are several factors that need to be emphasized:

a. A clear statement of the objective must be provided to the investigator.
b. The method of selection of animals must provide for adequate confirmation of the disease or clinical state present, and assignment to groups should be under conditions which exclude or minimize bias.
c. It must provide an outline and explanation of the methods of quantitation and observation of the parameters studied.
d. It should provide a description of steps taken to document comparability of variables such as age, sex, severity of disease, etc.
e. It should provide a description of the methods of recording and analyzing the response variables and the means used to exclude or minimize bias in the observations.
f. It should provide a precise statement of the nature of the control group. Possibilities are placebo control, active control and historical control.
g. It should provide a complete summary of statistical methods used in data analysis.

A new and interesting aspect of the pre-market review process involves the fact that NADA's must now contain information to allow an evaluation of the drug's potential effect on the environment. The manufacturer prepares an impact statement, BVM reviews this data and makes one of the following determinations:

1. The drug has no discernible effect on the environment.
2. The impact of the drug is marginal or insignificant.
3. The impact is considered significant. When the manufacture or use of a product poses an unacceptable threat (weighed against potential benefits) to the environment, it will not be approved.

The Bureau of Veterinary Medicine has a very active intramural and extramural research program which is designed to resolve one of the major scientific issues facing FDA today. This is the problem of drug residues in food animals. This problem crosses the entire spectrum of BVM activities, from pre-market review to post-market surveillance. It is a complicated problem, and based on our previous experience, it is one in which you as bovine practitioners must play a much more important role in the future. The laity, who are a major user of animal drugs, are becoming much more aware of the drug residue problem. However, they need the expertise and judgement that you as professionals can provide regarding the significance of drug residues. Maintaining a viewpoint that a little drug residue couldn't hurt anyone could become very detrimental to the future use of drugs in food animals. The problem

must be approached from a sensible and practical viewpoint, but must be balanced with concern for and by the consumer.

The Bureau of Veterinary Medicine research program is hopefully designed to allow us to accomplish this goal. It is basically comprised of five elements of effort:

1. To develop more data on drug dosage forms and route of administration and their impact on persistance of drug residues.

   Examples: 1) Three percent aluminum monosterate prolongs the excretion rate of drugs from intramammary infusion three fold - 72 hours versus 210 hours when compared to drugs in a 2% aluminum monosterate base or an aqueous dose. 2) DHSM in aqueous suspension given I/M causes residues for +90 days at inspection sites, but given sub/Q only causes residues for 30 days, and still gives equivalent blood levels.

   Research must be conducted which will delineate the dosage form and route of administration which will give (1) the necessary therapeutic effects and minimize the drug residue problem. (In the past, formulations were developed primarily on the basis that the vehicle provide good stability of the active compound.) (2) Veterinary drugs have historically been developed to provide long-term blood levels to minimize animal handling and repeat treatments. This concept may not be compatible with preventing or minimizing drug residue problems.
2. To determine the effect of animal variability on drug withdrawal requirements:
   Conventional methods for conducting drug residue studies

Drug Withdrawal Intervals

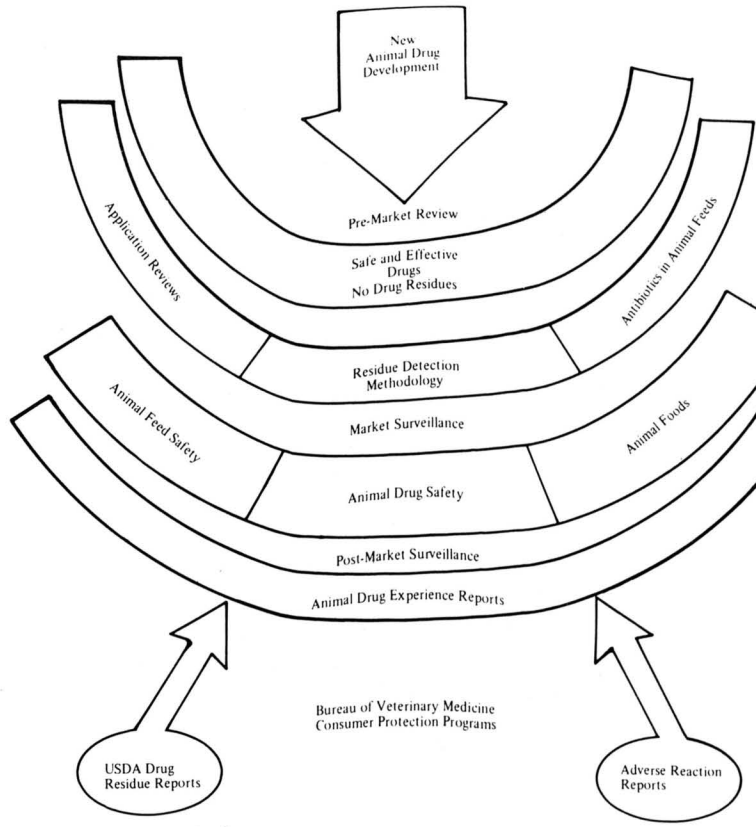
	Positive	Negative
Dose Normal Animals (Days)	0 3 5	7 10
Sacrifice (Animals)	3 3 3	3 3

Disadvantages of This System: Drug withdrawal based on three animals; no requirement to use standard animals; no work done on sick or diseased animals; and studies have to be repeated in their entirety in each specie for which the drug is intended.

Based on the results of recent research, we will soon be proposing a new system for conducting drug residue studies.

a. Pharmacokinetic drug modeling in the target animal (normal or diseased), i.e. determine the biologic half-life of the drug in major organs and body fluids, and determine the organ of concentration.
b. Devise a mathematical model for drug excretion - project a withdrawal period on this basis.
c. Select a sufficient number of animals (10-15) at the projected withdrawal interval and slaughter for verification.
   1. Animals can be salvaged if negative as expected.
   2. An adequate number of animals will be tested, and will be more representative of the population.
   3. Actual number of assays reduced.

Advantages: minor formulation changes may not require a major residue study - only a repeat of kinetic drug model; withdrawal period will be more precise; and will delineate the difference in drug metabolism between normal versus diseased animals.



3. Assay Methodology. Most of the drugs approved for use in food animals have an analytical or biological assay method developed. However, there are many deficiencies in this element. They fall into three main categories:
   a. Assay method developed but lacks specificity or lacks confirmatory methods.
      Examples: sulfonamides, thiabendazole, organic phosphorus compounds, neomycin, DHSM, and erythromycin.
   b. Inadequate or non-existent methods for drug assay in tissues.
      Examples: phenothiazine, piperazine, and tyrothricin.
   c. Drugs not approved for use in food animals, but are commonly used in food animal species.
      Examples: dexamethasine, tranquilizers (Phenothiazine Derivative), and chloramphenicol.

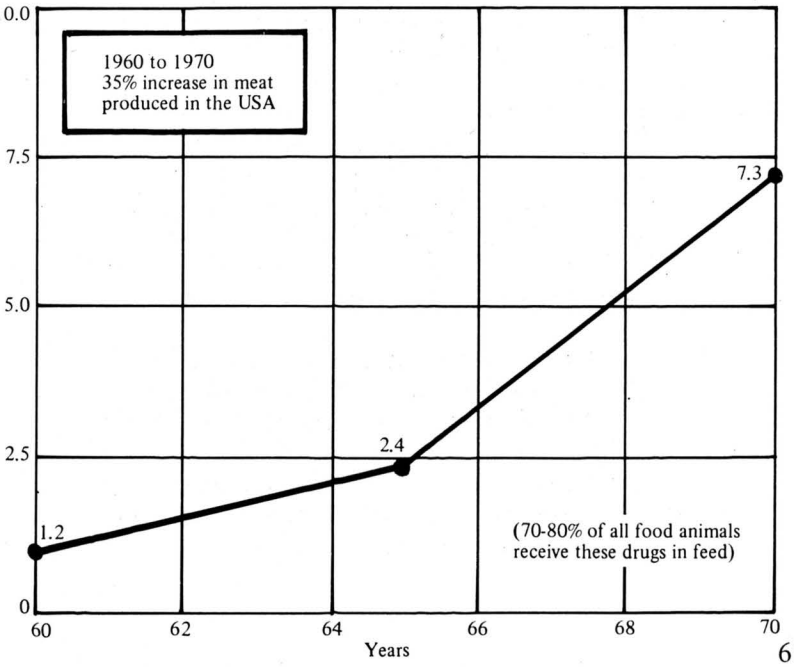
   It is obvious that at such time as methods are developed, then residue studies of these respective drugs will need to be conducted. Methods for dexamethasine, tyrothricin, and chloramphenicol are in the final stages of development and will be in use in the surveillance area in the near future.

Viewgraph II

4. Drug Residue Surveillance or Screening. Recognizing the fact that thousands of animals are slaughtered for human consumption each year, and only a limited number are examined for residues, has caused BVM to begin the development of rapid screening methods for detection of drug residues. It is envisioned that if such a system could be developed using, for example, urine as the basic excretion route, much larger numbers of animals could efficiently be screened for drug residues. We have initiated a research program for this purpose. The following methods, briefly described, seem to have great potential as economical screening methods.
   a. *Gel Electrophoresis.* Several antibiotics can be separated and the location of the antibiotics in the gel is determined by growing sensitive bacteria on the gel. Dyes may also be used to locate substances in the gel. Large numbers of milk or urine samples can be screened in this system.
   b. *Differential Light-Scattering Technique (DLS).* Antibiotics or other drugs are incubated with the sensitive strains of microorganisms for about 60 minutes. Then the control culture (not treated with drug) is compared to the cultures treated with several concentrations of the drug. The reflection of light scattering properties of the cultures are measured at several angles with respect to the laser source. The intensity of the scattered light is plotted versus the angle. The distance between the curves is proportional to the concentration of the drug. Can be used on urine, meat juice, serum directly. Works well for antibiotics, anticancer drugs, and other chemicals. Must have specific sensitive strains of bacteria for each chemical. It is estimated that 100-200 samples per hour can be run through this system.

Bureau of Veterinary Medicine

Comparison of Annual Use of Antibacterial Drugs for Animal Feeds in the United States



   c. *Thin-Layer Chromatography.* Rapid screening for sulfa drugs using TLC has been developed. Urine or serum is spotted directly on TLC plates. A TLC method for furaltadone in milk is available. Furaltadone is quantitated by densitometry at 370 nm.
   d. *High Speed (Performance, Pressure) Liquid Chromatography.* The high resolution of HPLC equipment will allow better separation of drug residues from other interferring substances in tissues. Several column packing materials are available including ion exchange resins which have successfully separated several sulfa drugs. Gradient elution from 100% of one solvent to 100% of a second solvent will allow the detection of a greater variety of drug residues in a single injection. After specific conditions are worked out on expensive research models, these conditions can be applied to less expensive models for field use.
   e. *Gas Liquid Chromatography.* Gas liquid chromatography may also be useful as a screening tool for sulfa drugs and nitrofurans.
   f. *Mass Spectrometer (MS) Fragmentation Patterns.* The mass spectrometer has been used as a detector for gas liquid chromatography for several years. Now MS is also being adapted as a detector for HPLC. In the MS, the drugs are fragmented into ions. A special monitor can be used to determine quantitatively ions from a drug. Up to three ions can be monitored at one time. The sensitivity is in the ppt range. This technique is presently being adapted to dexamethazone and cortisone. The fragmentation pattern for a pure compound under a specific set of conditions is very specific for a particular drug and can be used to identify the drug and determine the quantity present.
   g. *Radioimmunoassay.* If antibodies are specifically designed to determine whole groups of compounds such as all sulfa drugs (NH_2⬡) or nitrofurans (ON_2 ⬡⬡). These tests could be run on hundreds of urine or serum samples in a day and would give an idea of the residues present from a specific class or group of slaughter animals.

5. Significance of Drug Residues.
   a. Effects of cooking. Degradation and inactivation.
   b. Half-life of drug residues under frozen or storage conditions.
   c. Toxicological consequences of ingesting low levels of drug residues. AIBS contract to determine benefit versus risk of drug residues. NCTR project on steroid residues to develop toxicity models. Long-term chronic studies. Effects on enteric flora.
   d. Environmental Impact of Drug Residues. I believe this information should adequately serve to convince you that we at FDA con-

sider the drug residue problem in food animals to be of extreme importance. It should be understood by practicing veterinarians that when you inject or treat an animal with a drug of any description, you have established the possibility of that drug carrying through to the consumer. That practitioner bears the responsibility of informing his client of the importance of withholding that animal from market until any residues have cleared. This information is generally well established on product labeling. If not, then he must assume the responsibility of using that drug and possibly producing harmful and/or illegal residues.

The Bureau also has an active program in market and post-market surveillance of veterinary drugs. Adverse reaction reports are continously received by the Bureau. They are analyzed and their significance determined. If significant action is required, action is taken to modify the drug labeling, or removing the drug from the market. An active educational program is currently being developed by the Bureau to increase and improve communications with the practicing veterinarian.

Viewgraph III

In addition to these legislated responsibilities, BVM often becomes involved in special scientific problems. Three of the most notable and recent problems have involved (a) antibiotics in animal feeds; (b) review of mastitis infusion products and (c) contamination of animal feeds with industrial chemicals. Any one of these special problems warrants a lengthy discussion because of their importance to this group. Realizing that time is not available to adequately discuss these problems, I wish to briefly summarize their current status.

a. Antibiotics in animal feeds. The FDA has recognized that there are several potential hazards associated with the widespread use of antibiotics in animal feeds. The drug industries and FDA are in the process of developing extensive research data. The final results of these studies are forthcoming; however, I believe it is fair to state that data already developed indicate that certain restrictions and standards will be required for the future use of these drugs in animal feeds. Decisions regarding this matter will be made during the next 12-18 months.

b. Mastitis Infusion Products. Many articles have been published in which the Bureau of Veterinary Medicine is accused of depriving the dairyman and the veterinarian of safe and effective mastitis products. Speaking as a scientist and not as an FDA employee, I fail to find evidence that this is the case. In simple terms, the FDA for the first time in the history of mastitis infusion products are requiring scientific evidence to support the efficacy of these products. Thus, the number of kitchen sink, multiple ingredient mastitis infusion products are diminishing at a rapid pace. This seems to be alarming too many dairymen and veterinarians. It is not foreseeable that FDA actions will result in no products on the market to treat mastitis. What is foreseeable is that the few products which are supported by adequate efficacy data will remain available and will be reliable therapeutic tools in the hands of the veterinarian or the dairyman. We believe this to be essential in the control and treatment of this important and expensive disease.

BVM Programs

BVM Consumer Constituency	
Consumers of Animal Protein	210M
Farmers Engaged in Animal Production	705K
Poultry	57K
Livestock	648K
Veterinarians	25K
Livestock Population	
Animals Fed Annually	
Red Meat Animals	197M
Chickens (Broilers)	2.9B
Other Poultry	435M
Dairy Cattle	16M
Size of Regulated Industry	
Total Agriculture	$44B
Meat Industry	$22B
Prepared Animal Feed	$5.7B
Registered Feed Mills	12K
Registered Animal Drug Firms	650

c. Contamination of animal feeds with industrial chemicals. During this present calendar year, FDA and the Bureau have been faced with at least three major incidences of industrial chemical contamination of animal feeds. These were dieldrin, hexachlorobenzene, and polybrominated biphenyls. Tremendous losses have been incurred from these contaminations. We recognize this problem as being largely unpredictable, extremely wasteful of our food resources, and potentially hazardous to public health. We are attempting to devise methods to more adequately handle this type problem. As a practitioner, you must always be alert to this potential problem area and be prepared to objectively evaluate the circumstances.

I trust that this presentation has given you an overall view of the Bureau of Veterinary Medicine and the variety of responsibilities that we assume. We honestly encourage, and are actively promoting, an effort to make you, the practicing veterinarian, a more important member of this team.

Thank you.