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**SESSION 5: The Role of Academia in  
New Animal Drug Approvals**

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# FDA-CVM Drug Approval Process

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A drug for use in animals is reviewed and approved by the Food and Drug Administration's Center for Veterinary Medicine (FDA-CVM) on the basis of conclusive evidence that it is both effective and safe. The responsibility to develop and present that evidence belongs to the drug sponsor. When the drug is intended for use in food-producing animals, safety issues become extremely complex because it is not simply a matter of demonstrating that the drug is safe for use in the target animal, but also that food products derived from the treated animal do not contain unsafe drug residues. The process for obtaining approval of a new animal drug is complex, time consuming and requires extensive interaction between the sponsor and FDA-CVM.

## **The Regulatory Requirements**

The animal drug industry is regulated by several sections of the Federal Food, Drug and Cosmetic Act (FFD&CA). While the first law enacted by Congress for the purpose of protecting the public against adulterated or unwholesome food went into effect in 1890 (Wiley Act), being significantly strengthened in 1906 and 1912, it was in 1938 that the basic Federal Food, Drug, and Cosmetic Act, as we know it today, came into being. Since that time, there have been several modifications, the most important to our business being the Kefauver-Harris Amendments of 1962 and the Animal Drug Amendments of 1968. The enactment of these latter two amendments has resulted in the basis for the regulation of animal drugs in the manner we know today.

When federal agencies become involved in regulating some aspect of our society, they obtain their authority from the specific laws passed by Congress. They then develop regulations to elaborate the law and provide more detail as to how the law will be interpreted and implemented by the Agency. The regulations developed by FDA, as a federal agency, to implement the FFD&CA are contained in a multi-volume called Title 21 of the Code of Federal Regulations (21 CFR).

The regulations contained in this document are, in essence, as binding as law. The procedures for adding, deleting, or revising regulations contained in the CFR are very precise, in many cases being as laborious as those involved with the enactment of legislation by Congress.

The laws and regulations, however, seldom define precisely what the FDA-CVM requires in specific situations for their actual implementation. When it appears to be desirable to better define how the FDA-CVM plans to specifically interpret various requirements, it will develop and make available guidelines. Guidelines are intended to be just what their name implies. They are not laws or regulations, but specific suggestions as to how the FDA-CVM believes a specific issue should be satisfied. However, while they are not as binding as law, one needs to have an acceptable and justifiable alternative if one is to deviate from them. Guidelines then become the real criteria a drug sponsor must satisfy when developing a new drug for animals. When those animals are food-producing animals, the guidelines become very specific and, generally, quite rigid. The reason for this, of course, is that FDA's greatest

responsibility to the public is to protect its health by making sure its food supply is as safe and wholesome as the public believes it to be.

## **The Data Requirements**

The data that must be developed and submitted for review by FDA-CVM before a drug is approved for use in animals are defined in 21 CFR. Specifically, the requirements are spelled out in 21 CFR Part 514 and are included in an official FDA document called the Form FDA 356V, or New Animal Drug Application (NADA). The NADA contains eleven (11) major sections, and dozens of sub-sections, all of which have to be satisfied before a drug may be approved.

Following are the major sections of the NADA, along with a brief summary of the information called for in each, and thus, a description of what is required for drug approvals in animals, specifically those used for food:

**1. Identification** - This simply identifies what kind of application the sponsor is submitting, including a brief description of the drug and the sponsor's name and address.

**2. Table of Contents and Summary** - Describes the organization of the application and a summary of what it contains, including the scientific rationale and purpose of the drug, highlights of the research conducted, evaluation of the data, and the conclusions reached. In short, upon reading this section, one should be able to understand what the sponsor is proposing and on what basis the proposal is made.

**3. Labeling** - The basis for any drug approval is its label. This is the information on which the user will have to depend to properly use the drug. Therefore, it must be complete, accurate, clear, and totally consistent with the data from the research conducted to support the approval.

**4. Components and Composition** - This defines the ingredients that make up the drug product and how they are put together to make the final formulation.

**5. Manufacturing Methods, Facilities, and Controls** - This is a very complex section which provides a complete description of how the product is produced, the facilities and equipment used, the qualifications of the people involved, the specifications and test methods for all the raw materials and finished product, description of and test methods for all the packaging components, stability data, and an environmental analysis of the manufacturing process. For each pivotal study, the sponsor must utilize the same formulation manufactured using the same process described in this section.

**6. Samples** - This section provides for the submission of samples of raw materials or finished product for testing purposes when required by FDA.

**7. Analytical Methods for Residues** - This is one of the major sections of the new drug approval process which are unique to food producing animals. Basically, it requires the development of an analytical procedure to detect minute levels of residues of a drug or its metabolites, and the establishment of a withdrawal period to assure the public does not inadvertently consume potentially harmful chemicals. While these are the primary goals for this section, the research to achieve them is very complex and expensive, and will be addressed again later.

**8. Evidence to Establish Safety and Efficacy** - The research designed to determine if the drug has the effect claimed on the label and is safe to the animal treated, is conducted to satisfy this section of the requirements. It is through this work that a dose is established, the treatment period determined, the margin of safety determined, and the nature of side effects

and/or adverse reaction identified. Most of the information included on a product's labeling comes from these studies.

**9. Good Laboratory Practice Compliance** - A statement of compliance or non-compliance (with reason for non-compliance) to good laboratory practices of each nonclinical laboratory study.

**10. Environmental Assessment Report** - This must be prepared for all NADAs; however, for food producing animals, a comprehensive report must be prepared, detailing the potential effect of the subject drug on the environment. Generally, this will involve research studies which are designed to evaluate the effects of a drug, when used as labeled, on the soil, groundwater, lakes and streams, plants, normal environmental bacteria, wildlife, etc. It involves a detailed understanding of the fate of a drug in the animal and the exposure of the environment to the drug through the animal's excretions. Depending on the drug and its use, this can be an extremely complicated issue to resolve. Material Safety Data Sheets (MSDS) and references to various state and federal manufacturing related permits are also part of the EA document.

**11. Freedom of Information Summary** - To comply with regulations based on the public's "right to know" what is going on in regulatory agencies, a Freedom of Information (FOI) summary is prepared for public disclosure. This FOI summary becomes probably the single most important piece of the NADA, since it is made available for public use. It must include rather detailed summaries of all the data on which approval of a product is based, and, therefore, must be legally defensible. For this reason, it is highly scrutinized by FDA lawyers, making sure that, if challenged, its contents may be defended in court.

## The NADA Review Process

Once all the data is generated and the NADA assembled, a process that for drugs intended for food animals will have taken an average of 5-8 years, it is ready for submission to FDA for review. FDA is mandated by regulations to respond to any NADA within 180 days. However, when that first response is received in about 180 days, it invariably is in the form of an "incomplete letter". FDA utilizes this letter to indicate what data in the sponsor's application is not acceptable or is incomplete, and defines the deficiencies that must be rectified.

Depending on the nature of the deficiencies, the response from the sponsor could occur anywhere from a few weeks to a few years. Many times, additional research may be required, in which case, the response will take months to years for the sponsor to generate data and prepare a response. This whole process is repeated a number of times until FDA accepts the sponsor's application and approves it. (Note: Most NADAs involve three to six "incomplete letter" response cycles encompassing a period of three to five years). Thus, from the time it is determined that a drug has a particular activity, is developed for a specified use and approved by FDA, it is not unusual for seven to ten years to elapse, at an expenditure of one to several millions of dollars.

Before a sponsor conducts a study that will be used to support a component of an NADA (i.e., a "pivotal" study), a drug sponsor is encouraged to submit a protocol to FDA-CVM for review and acceptance. Sponsors are expected to follow applicable FDA-CVM guidelines in the development of protocols. If a sponsor chooses to deviate from guidelines, justification must be provided to FDA. Additionally, if a sponsor chooses not to submit a protocol for review they proceed at a higher risk; in other words, the potential that FDA-CVM will reject the study increases. To achieve CVM's "approval" of a protocol generally

requires several correspondences and more than 100 days.

In the wake of the human generic drug scandal and various federal investigations, FDA-CVM has dramatically increased attention to data quality assurance issues. When pivotal studies are conducted, the sponsor must have systems

in place to assure both the quality and integrity of the data that is generated. FDA-CVM requires drug sponsors to strictly adhere to standardized practices (e.g., protocol adherence, raw data documentation) for conducting studies. These standards are defined in Good Laboratory Practices (GLPs) regulations and in "Good Clinical Practices" (GCPs) guidelines (as defined in the 1992 clinical investigator guidelines). If a study does not meet the quality assurance standards that FDA has defined, it is unlikely that the study can be used to support NADA approval.

Pivotal studies must be conducted to prove that a drug is efficacious. These pivotal studies must document both a dose-response relationship and efficacy under conditions of use (multi-location clinical trials). The time that pilot dose determination studies are conducted to the time that a sponsor and FDA-CVM reach concurrence on a dose often encompasses a period of more than two years. This time period is very significant because target animal safety studies and clinical (field efficacy) trials cannot be conducted until a dose has been established. After an NADA is approved for a species, the dose determination process must be repeated for each new indication in that same species.

The use of pharmacokinetic and pharmacodynamic data to establish the efficacy of animal drugs is receiving increasing attention. Presently, FDA-CVM regulations and guidelines do not specifically address this topic; however, FDA-CVM is working with the veterinary profession and pharmaceutical companies to develop guidelines that will determine how such data can be utilized in the drug approval process. To this end, CVM recently published their "Points to

Consider" document in the Federal Register. Although guidelines have not been developed, FDA-CVM currently work with sponsors to utilize this type of data in support of the efficacy component of NADAs. Ultimately, however, a drug sponsor's decision to select pharmacokinetic studies over traditional efficacy (dose determination) studies is contingent upon the amount and type of data that will be required by FDA-CVM under their pharmacokinetic guidelines.

## Human Food Safety

When you and I as consumers buy animal food products at the supermarket, we assume them to be safe and wholesome. We do not want them to contain residues of drugs that may be harmful if consumed. You, as producers, do not wish to market livestock which may contain harmful drug residues. We, as drug manufacturers, want to know the safety and residue picture of our products so that they may be labeled for safe and effective use, and, of course, FDA wants to be sure the public is protected and remains confident in the wholesomeness of its food supply.

The key factor to consider is the assumption by the consumer that its food supply is safe. If we buy cigarettes, we buy them with the full knowledge, because of mandatory labeling, that they are harmful to our health. When we use drugs directly ourselves, we are told either by our doctor or pharmacist, or by the labeling of the drug, what risk we are taking along with the drug. In both cases, we make informed decisions with full knowledge of the risks. However, we partake of our food supply with a different attitude. We assume it's safe. We acknowledge no risk. Therefore, the producer, processor, feed and additive suppliers, and the regulatory people all have a responsibility to see to it that it is in fact safe, and that the consumer's trust is not violated.

As mentioned previously, the drug manufacturer's responsibility for food animal drugs involves the development of an accurate and adequately sensitive

analytical method to detect very small levels of drug in meat and milk, and then the establishment of an adequate withdrawal period to insure against inadvertent consumption of harmful residues. These two activities are tied closely together and both relate to the basic problem of establishing what is a safe tissue level of residues of a given drug.

In dealing with the challenge of establishing a safe level of a drug in tissue, and ultimately an appropriate withdrawal period, several activities are systematically addressed:

**1. Threshold Assessment (TA)** - The chemical is subject to several types of assessment to determine the extent of testing necessary to assure safe use. In general, the decision becomes one of whether or not the chemical has the potential to produce tumors (carcinogen). If it does, then it is handled in a much more severe manner, and may never survive the rigid criteria established. The purpose or intended use of the chemical also plays a major role in its assessment (e.g. a drug used on a herd basis for routine use as a growth promotant will have more rigid requirements than one used on individual animals to treat a specific disease). The third part of the assessment involves the determination of total drug residues through the use of radioactive drug studies. This measures the total of both the drug itself and its metabolites. The higher the total residues, the more severe the requirements.

**2. Toxicological Testing** - Depending on the outcome of the Threshold Assessment, a series of toxicological tests are conducted in various species of laboratory animals such as mice, rats, dogs, sub-human primates, or other special species as indicated. These studies may range from specialized short-term studies to 30-day, 90-day, 10-year, 20-year, and lifetime studies, depending on the perceived need based on the TA. It's important to recognize that the purpose of these studies is not to determine safety in

the species tested, but to try to predict the expected safety concerns for man, attempting to establish the highest level which causes no effects. Once the highest no-effect level (NOEL) is determined, then a 100X or 1000X safety factor is applied to further assure safety to man.

**3. Metabolism Studies** - These become some of the most complicated and expensive studies to conduct and interpret. The objective is to determine the disposition of the drug in the animal, i.e., is it broken down to metabolites or does it pass through the animal unchanged? The purpose is to identify what chemical should be used for toxicology testing and as the marker compound for residue testing. Sometimes a metabolite is more toxic than the parent compound, so in such cases it obviously would not do any good to conduct the toxicology studies with the parent drug. Also, metabolism studies involve identification of the target tissue (e.g. liver, kidney, fat, etc.) in which the highest and longest residue level of the drug is observed.

**4. Establishing a Tolerance** - Based on the results of the metabolism studies, the toxicology studies, the highest no-effect levels, the safety factors applied, the target tissue, and an arbitrary consumption value, a tolerance, or safe concentration in tissue is established.

The conclusion is that the consumption of food products containing the tolerance level or safe concentration of a drug and its metabolites would be completely safe.

**5. Method of analysis for Residues** - Once the marker compound, target tissue, and tolerance are established, then a method of analysis is developed so that the food supply can be monitored for residues of the subject drug. This allows the USDA (FSIS) to monitor a particular drug so we can be assured that violative tissue residues are not contaminating our meat and milk supply.

**6. Establishment of a Withdrawal Period** - Finally, it needs to be determined how long a drug must be withdrawn from an animal prior to being slaughtered for food or milk being sold for human consumption. This assures that no residues in excess of an established tolerance level will exist in food products. Using the established method of analysis, tests are conducted on animals sacrificed or milk collected at various times after withdrawal. The withdrawal period then becomes the first sampling time that all samples are either negative or below the approved tolerance or safe concentration. This period then becomes part of the approved product labeling, that when followed, assures safe use of the drug.