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**SESSION 2: Veterinary Pharmacology in  
Animal Health Pharmaceuticals**

Chairperson  
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# What It Takes To Get Animal Health Pharmaceutical Compounds To The Market

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Developing an animal health product is a complex, time-consuming, and expensive process. In many ways, it is even more complicated than developing a human health product.

The animal drug regulatory requirements are very complex and stringent, especially for a food-animal indication. For the purposes of this presentation, I will try to concentrate on a food-animal approval for a therapeutic drug. The process for a non-food animal product approval is similar, except that human food safety studies are not required.

To obtain an approval in the US, the sponsor must submit a New Animal Drug Application (NADA) which should include studies to show that the drug is safe and effective for the intended use in the target animal. In addition, for a food animal claim, the NADA must contain data showing the safety of the drug and its metabolite residue profile in order to establish a withdrawal time for human consumption. The potential environmental impact of the drug and its metabolites also should be established.

A typical NADA will have 11 sections. These are:

- 1 Introduction
- 2 NADA summary
- 3 Proposed label text for all packaging components.
- 4 Listing of all components of the new animal drug.
- 5 Full description of manufacturing including facilities, equipment and personnel involved in manufacture, testing and packaging. Also stability data to support proposed shelf life.

- 6 Statement regarding availability of samples for testing by Center for Veterinary Medicine (CVM).
- 7 Human food safety studies (laboratory animal toxicology and metabolism) and target species residue depletion.
- 8 Target animal safety and efficacy studies.
- 9 GLP certification statement for safety studies.
- 10 Potential environmental impact of both the manufacture and use of the product.
- 11 Summary of all data (Freedom of Information summary).

New drugs are discovered in a variety of ways. On the human side, they are usually the result of a very targeted design or discovery effort. Very few animal health companies have any dedicated discovery efforts in designing new compounds. The majority of non-anthelmintic animal health drugs on the market today are an offshoot of human drug research.

Due to the huge expense of developing an animal health drug, the small probability of success and the limited market potential compared to human drugs, I do not see any major increase in the dedicated discovery effort in the animal health field. In fact, worldwide, there are only 10 animal health pharmaceuticals with sales of over \$50 million.

Once a compound has been identified to have some therapeutic application or potential, feasibility studies are conducted before a recommendation is made for development. These would include *in vitro* and *in vivo* model studies, pharmacological studies and limited

formulation and blood level studies in the target animal. If the compound still holds promise, Marketing Department input is sought on the sales potential.

Table 1 shows the time and costs involved in developing various compounds for food animals.

Based on the sales potential and anticipated research expenditure, a decision is made whether or not to pursue the project. In order to stay in business, the pharmaceutical manufacturer needs a return on this investment in 3 to 5 years.

A large number of people are involved from the beginning of a project, with one person designated as the leader for the project (Figure 1). This person is responsible for making sure all aspects of the project proceed in a coordinated fashion. Any unexpected result or change of course is brought to the attention of upper management, where go/no-go decisions are made for project continuation.

In order to conduct the required studies to complete the NADA, an Investigational New Animal Drug (INAD) file must be established with the CVM. The INAD allows an exemption for unapproved animal drugs to be shipped interstate for the purposes of conducting these studies.

The requirements for establishing an INAD include preliminary target animal safety and efficacy data on the drug, as well as preliminary environmental and human food safety information.

The typical development program for a compound is given in Figure 2. This assumes that everything goes according to plan and no studies have to be repeated. As you can see, it takes a minimum of five years to complete the studies required for a food-animal NADA. There are a number of milestones during this development timeframe, *e.g.*, it is prudent to have CVM review the dose titration studies before beginning clinical field trials.

In the next few paragraphs, I will describe the details of the following sub-projects:

1. Efficacy and safety
2. Toxicology
3. Metabolism and residue chemistry
4. Regulatory Affairs

## Efficacy and Safety

Efficacy and safety of the product must be established in the target animal (Figure 3).

A dose titration study is usually conducted in either an animal disease model or in the natural outbreaks of the intended disease claim. These studies should be conducted preferably with the final formulation.

At Schering-Plough, we like to confirm the dose from the dose titration studies in dose confirmation trials. During this time, we also submit the dose titration studies to the CVM for their review so that field clinical trials can be initiated as soon as a dose is approved by the CVM. Being a multinational company, most development programs we have are for 10 or more markets, and local clinical field trials are needed in these markets for regulatory approval.

Various safety studies conducted are listed in Figure 3. These studies are conducted with the final formulation and are based on multiples of the intended dose defined in the dose titration studies, in order to establish the margin of safety.

## Toxicology

The toxicology part of the program is the most expensive and time-consuming. These studies are conducted in a certain chronology because information regarding dose levels, etc., is needed from short-term studies to initiate longer term studies.

We start with the genetic toxicology program to determine the genotoxic potential of the compound. Based on these studies, along with data from subacute studies and comparison of the compound structure to the FDA structural guide for carcinogens, it is determined whether or not carcinogenicity studies are needed.

The studies listed in Figure 4 are either required by CVM, international regulatory bodies or both. The studies are conducted, taking into consideration the individual study requirements from the worldwide regulatory authorities.

The last two studies on this slide, carcinogenicity bioassays in rats and mice, are the most expensive studies. Each one costs approximately \$1 million and takes 3 years to complete. These studies are usually rate-limiting to the completion of a program and cannot be initiated until information is available from the short-term studies to determine the dose levels for these studies.

## **Metabolism and Residue Chemistry**

The studies required in the metabolism/residue program are listed in Figure 5. This part of the program is also significant in terms of cost and time. The overall goals are to show a) comparative metabolism between the target species and the laboratory species, b) total residue depletion of the radiolabelled compound in the target species, c) identification of the marker residue and target tissue, d) development of surveillance and confirmatory assays for the marker residue and e) final residue study to establish a withdrawal time.

## **Regulatory Affairs**

The Regulatory Affairs department is involved at the start of any program. They provide guidance regarding the regulatory requirements needed to complete the registration of a particular compound.

They act as liaison and primary contact between the company and FDA CVM. It is important to involve them early in the development of a new animal drug in order to 1) avoid conducting unnecessary studies or 2) avoid a deficient NADA submission.

**Table 1**

Product	Species	Discovery to Marketing	
		Time	Cost
Growth Promotant (Feed)	Poultry	8 years	\$14 million
	Swine	9 years	\$14 million
	Beef	10 years	\$18 million
Coccidiostat (Feed)	Broilers	7.5 years	\$14 million
Anthelmintic (Dosage form)	Beef	8 years	\$16 million
Estrous Synchronizer (implant or injectable)	Beef	10 years	\$8 million

Ref: Flick 1987, Symposium Proceedings, Dollars & Sense, Herndon, Virginia

Figure 1

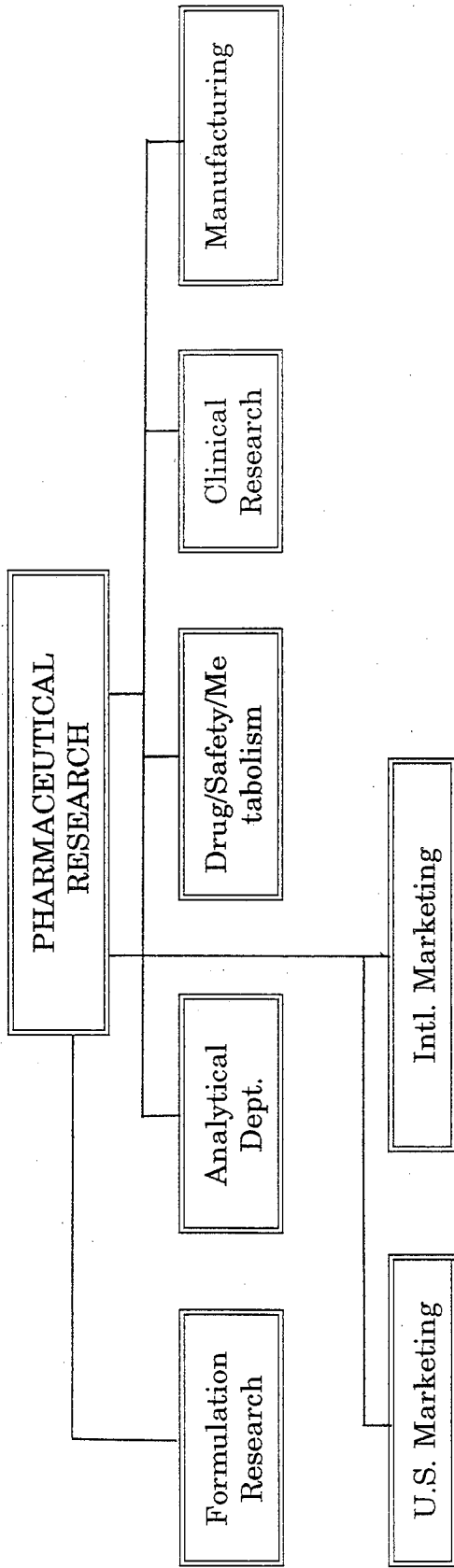


FIGURE 2

COMPOUND X  
DEVELOPMENT PROGRAM

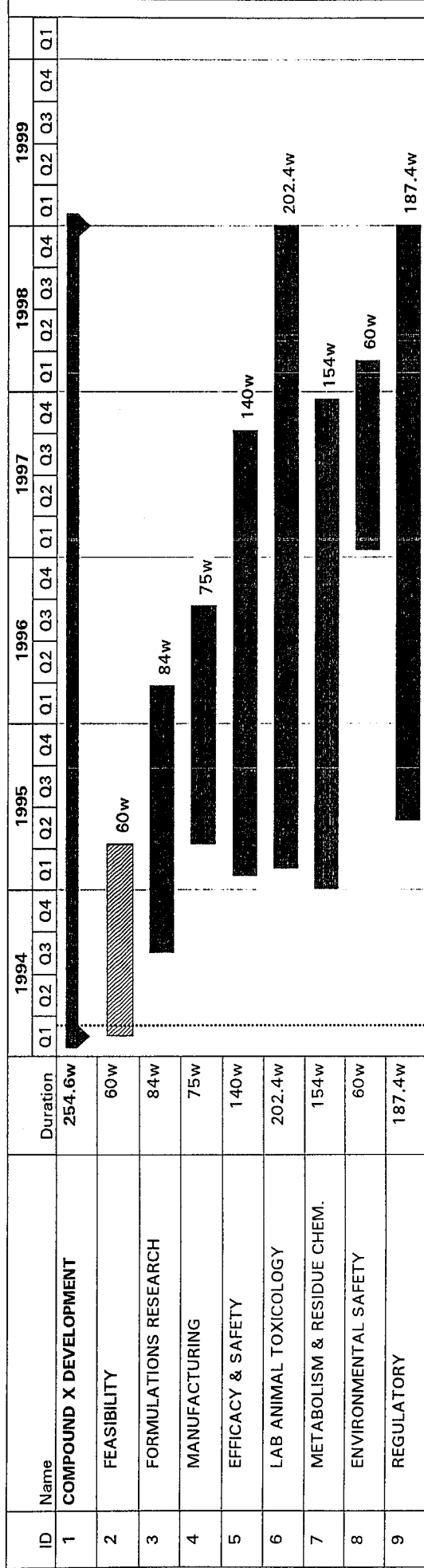




Figure 4

Schering-Plough Animal Health  
Compound X

