

DR. MILLER: Thank you, Dwight, for an interesting talk. Our next speaker is going to address "The Impact of Dose Determination on Development of Animal Drugs." Dr. Rainer Muser, from the American Hoechst Corporation, is a graduate of the University of Munich in 1957. He was very active in the Diagnostic Institute at Heidelberg, Germany, and was Deputy Director of that Institute until 1969 when he joined Hoechst. He is currently Director of Research and Development for the American Hoechst Animal Health Division. Rainer...

DR. MUSER: Good morning. It's a distinct honor to be included in this illustrious rostrum of speakers here and I really look forward to these two days of lively discussions. And I know it will be lively!

The Impact of Dose Determination on Development of Animal Drugs

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The development of drugs for use in animals can be seen as a series of decisions which are based on preplanned and coordinated work. As a whole, the preparations for the introduction of a new animal drug are a complex network of interrelated activities and decisions. Because the decisions are interrelated, many aspects have to be kept in mind when one activity is initiated or completed. The determination of a dose for a new animal drug cannot be based only on any one individual aspect such as efficacy, safety, economics, residues in edible tissues or formulation. However, the impact of some of those factors may be more powerful than that of others. Depending on the viewpoint of the individual contemplating the dose recommendation, different factors may seem more significant. For instance, from the drug manufacturer's point of view, the time factor in the development of a new product is an important economic consideration. It is the responsibility of the drug manufacturer to make a decision acceptable to the reviewing Food & Drug Administration (FDA) but also, and most importantly, a decision which renders a useful drug acceptable to the veterinarian and/or end user.

The purpose of this paper is to contribute to a discussion which will result in recommendations how to determine suitable dose levels of new animal drugs without some of the problems that have occurred in the past.

When dose determination and the development of animal drugs are discussed, different types of drugs or perhaps even individual drugs must be considered separately, for instance, production-type drugs and therapeutic drugs must be studied differently as their purpose differs. Antimicrobial drugs which will occupy a major portion of this symposium include good examples of both types of drugs. This paper will address only therapeutic drugs but its conclusions should also have a more general meaning. Antimicrobials are also good examples for a discussion of the measurement of activity or more specifically, efficacy, because it can be measured relatively easy in-vitro, but not so easily in-vivo. Quite a few of the factors to be considered in the determination of an effective dose can be very well illustrated with data collected in the development of antimicrobials.

From the point of view of a drug manufacturer, four theses are proposed:

1. A dose determined for a new animal drug designated for therapeutic use should be safe and effective.
2. Safety and efficacy should be the only consideration of the reviewing FDA.
3. Cost considerations with an attempt to keep the dose levels low assuming that this would save the end user money should not be the responsibility of the FDA. This should be left to the strongly regulating forces of a very competitive market.
4. There are good reasons in some instances to recommend initially a higher level with an option for lower doses when experience permits or to recommend a flexible dose range that can be adjusted to individual requirements.

There are basic steps in the determination of a suitable dose which are part of every development plan for a new animal drug and can be anticipated assuming an ideal course of events.

Preliminary Studies

When a compound is selected from screened substances for further development, its principle activity is known. Studies in-vitro and in laboratory animals are used to gather initial information about the efficacy and safety of a new compound. Minimum inhibitory concentration in-vitro with antimicrobials, controlled critical studies in target species with anthelmintics, pharmacological model studies, pharmacokinetic studies may be done in that phase including studies of general residue patterns in food producing animals which may also be considered pharmacokinetic studies.

The development of an animal drug will be different from that of a human drug in that phase since target species animals may be used instead of laboratory animals. Regardless of the method used, a tentative dose level should result from this stage of investigation.

Confirmation Studies

The tentative dose identified in preliminary studies needs to be tested under controlled conditions in different settings to determine if variables, as for instance, different strains of pathogenic microorganisms, different breeds of animals and so on influence the results of drug treatment. Drugs intended for food producing animals will be studied more thoroughly for residue depletion and metabolism in preparation for clinical studies. Detailed safety studies in the target species will be started at this point. A final formulation needs to be designed. These studies may take place in a laboratory setting or under field conditions.

Clinical Studies

The selected dose needs to be further evaluated in larger numbers of animals, perhaps under less tightly controlled conditions, to build a data pool concerning the performance of the drug under a number of different conditions.

In food producing animals, clinical studies cannot be done until a withdrawal time has been set by the FDA.

These factors need to be considered individually or in combination when determining a dose for an animal drug:

Efficacy

A therapeutic drug has to produce the desired effect under all conditions that can be reasonably anticipated. Interfering factors need to be identified as much as possible and must be spelled out for the user. There are several reasons why a dose may have to be adjusted for efficacy as studies progress: the drug may behave differently under various conditions in-vivo than expected based on in-vitro or preliminary studies. The drug effect may differ in sick animals compared to healthy animals in which preliminary studies were done. There may be differences in the pharmacokinetics and metabolism with an effect on the behavior of the drug in various animal species, various breeds of the same animal species and different types of animals (different management, diet).

Pharmacokinetic and metabolism studies will reduce the chances for total surprises once the drug is used in a larger population, but important observations may be made as the number of animals treated with it increases.

Increasing the dose usually increases the effect. From this point of view, there is no reason to select a dose at the lower end of the dose effect curve (minimum effective dose).

Safety

A supreme principle of drug therapy has been nil nocere (Paracelsus). However, more recently, medical science has begun to weigh risk (of side effects) against benefit (desired effect). This is particularly true in the treatment of life threatening diseases in human medicine, but also in veterinary medicine.

However, with animal health products, the safety concern extends not only to the treated animal (target species) but also to the general public consuming food derived from treated animals. Here, the principle of nil nocere, particularly when used in the political arena, can turn into a nightmare for anyone who wants to develop a drug for food producing animals. It is very difficult to establish a risk-benefit ratio in this context since politically, the principle of zero risk is an impressive slogan. Currently, time and resources needed to collect information summarized as "human safety data" far exceed what is needed to demonstrate efficacy and safety in the target species.

Safety considerations may dictate a lower dose than desirable from an efficacy point of view, particularly if a narrow safety margin exists, or if unacceptable residue levels would result. These change may become necessary as the development of the drug progresses. In extreme cases, safety considerations may terminate the development of a drug.

Because residue studies play such a crucial role in the development of animal drugs and because they are very time consuming, they must begin

early. According to the current rules, it is not possible to support a New Animal Drug Application (NADA) with residue studies using a dose level lower than that recommended in the NADA.

However, it is possible to do residue studies with a dose level higher than the final recommended dose if the drug sponsor can accept the conditions associated with the higher use level (longer withdrawal time, higher costs and so on). Obviously, there are limits as to how high a projected dose can be set for the purpose of residue studies.

Target species safety studies with a finite design can only begin after a dose has been fairly well identified, particularly, if a drug has only a narrow safety margin. A drug sponsor usually will allow for some extra margin in the selection of the highest dose tested, however, this is not always possible or feasible.

Economic Considerations

The Animal Health Market is very competitive, the cost of a drug to the end user is a consideration more critical for success or failure than in human medicine, especially as far as drugs for farm animals are concerned. The market regulates itself by acceptance or rejection of new products. Drug manufacturers are acutely and sometimes painfully aware of these regulating forces. There is no need for authoritative regulation.

With nutritional products, economic considerations are more pronounced than with therapeutic products because nutritional products are designed to produce economic benefits in healthy animals.

Feasibility of Administration

Depending on the purpose of the drug, the route of administration may be dictated. Oral use may be preferred over parenteral use although the needed amount of drug may be greater. On the other hand, it may be unreasonable to exceed a certain dose volume and, therefore, the regimen may have to be modified: parenteral use instead of oral use may be recommended, repeated dosing may be chosen over single dosing.

With all these considerations in mind it is clear that there may be reasons why the lowest conceivable dose may have to be chosen: narrow safety margin, economic considerations, practical dose volume. But, this is justified only if acceptable efficacy is achieved.

However, it is also clear that a dose reasonably close to what will be the final recommendation must be determined early in the development of a drug. Some activities cannot be initiated with a reasonable approach unless a dose is set. The selected dose will have a direct impact on these tasks:

Finite Residue Studies in the Target Species

Residue studies include those designed to trace total residues usually with a radiolabeled drug. Analytical methods developed to demonstrate presence or absence of residues must be applied in studies with animals treated with the recommended dose. The possibility to study doses higher than the final recommended dose was mentioned earlier, but there are limits to that approach.

Formulation

A formulation for commercial use can only be designed after a dose has been determined. This is true not only for the design of fixed dosage forms (tablets, capsules, other single dose units) but also for any other dosage forms including injections or other liquids in order to arrive at a practical dose volume. Of course, other properties of the drug must also be considered.

The dose is important in designing the formulation, because the final formula must be suitable to treat an animal with the recommended dose by the recommended route. Excessive dose volume is undesirable, but on the other hand, a dose volume which is too small may also be impractical. The final dose must be easy to calculate. The needed accuracy of the calculation depends on the safety margin of the drug. From a practical point of view, the dose calculation can only be as accurate as information on which it is based. Many times, the body weight is estimated or a group of animals is treated with an average

dose. Therefore, the recommended dose must be high enough to compensate for errors occurring under field conditions. A dose at the low end of the dose efficacy curve could result in failure of treatment.

The drug concentration in the final formula must be chosen with these considerations in mind.

When the NADA is submitted, the drug sponsor needs to include sufficient stability data which can only be collected with the final formula in the final container. It is evident that the stability studies cannot start before the final formulation is established based on the dose recommendations. Stability data allowing a reasonable shelf life of the drug, usually at least one year, must be available before a drug can be approved.

Clinical Field Trials

Clinical field trials in food producing animals can only be initiated after an Investigational New Animal Drug Application (INADA) has been approved. This requires the conduct of specific studies, evaluation and submission of the obtained data to and review by FDA. The data need to be relevant to the recommended dose used in the final formula of the drug to be evaluated in the clinical field trials. This is a very time consuming process.

In summary, all considerations point to the need for determining a dose early in the development of a new animal drug. If adjustments of the dose are necessary, it is easier to make them downwards, it is next to impossible to increase the dose after studies supporting a lower dose have been completed unless a new series of studies is done.

The conclusion should, therefore, be that only safety and efficacy should be primary concerns when FDA/BVM reviews new animal drug applications for therapeutic compounds. From a practical and a scientific point of view, selecting the minimum effective dose is not a sound rationale for dose selection. Economical considerations should be left to the sponsor who will be subject to the regulating forces of the market.