Experimental Design of Clinical Trials with Combination Drugs

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When a sponsor evaluates the potential of pursuing a combination of two or more drugs for eventual approval by Center for Veterinary Medicine (CVM), one must first consider the goals of combination drugs. One of these goals is improved efficacy on a single disease state or improved efficacy for a product by increasing the number disease states on which it is capable of demonstrating therapeutic efficiency. Another goal may be improved safety, whether it be safety for the target animal or safety for the human as demonstrated by reduced drug residue concerns. Lastly, and probably one of the more important goals is convenience for the veterinarian and/or the producer. The ability to utilize a single formulation containing more than one drug ranks high on the desirability list for the ultimate user.

There are several considerations that a drug sponsor should evaluate prior to embarking upon pursuit of a formulation containing two or more drugs. Experience dictates that each formulation of combination drugs is unique. The uniqueness may be in the areas of pharmacy, efficacy, safety, or any of the areas that one considers in the pursuit of a single drug. Is the combination drug formulation justifiable? This is the most important factor as it relates to CVM. CVM is currently reviewing combination drug applications under guidelines published in October, 1983. These guidelines ofttimes are interpreted as the law rather than guidelines for pursuit of combinations. CVM's strict adherence to these guidelines ofttimes lead drug sponsors to the opinion that avoidance of combinations is most desirable. CVM's approach to drug combinations may prevent rational therapies that could benefit particular animal populations from reaching the market place. The ease of pursuit of data with combination drugs is impacted very heavily by the label claim or claims that are desired by the sponsor. Combining of two drugs with different claims is much less difficult than pursuit of combining of two drugs with similar claims. Another area to consider is the pharmaceutical aspects of the combination. Is the combination pharmaceutically feasible? It may not be possible to combine two drugs for potential oral and/or parenteral use as dose form products. The need for dose determination impacts heavily also when considering combination drugs. Dose determination is not usually required when combining two drugs wtih different claims, specifically if each drug

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has been approved by CVM prior to embarking upon combination studies. However, CVM's current stance dictates that dose determination is essential for combining of two drugs with similar claims. And depending upon the magnitude of the experiment and the precision of the observations that are made in the experiment, it may be very difficult to demonstrate that each drug in the combination provides a benefit. Lastly, one must consider the clinical trial protocol. However, a protocol for drug combinations is essentially the same as the type of protocol that one would utilize in pursuit of a single drug formulation. However, adherence to the protocol and precision of observations by investigators are extremely important when evaluating combination drugs because of the potential for very small differences among treatment groups. Examples of potential combinations that a sponsor may wish to pursue by combining two or more drugs in a formulation are given in Figure 1.

The goals of clinical trials for combination drug formulations are basically the same as those for pursuit of a single drug formulation. For a single drug formulation, clinical trials may be utilized for dose titration determinations. However, the 1983 AAVPT symposium on dose determination outlined that clinical trials are ofttimes less than desirable for pursuit of dose titration data. However, clinical trials are the only way that one can demonstrate field use efficacy and safety whether it be for a single drug or a combination drug formulation. Goals of clinical trials for combination drug formulations may or may not include dose titration. Clinical trials may be utilized as a means to achieve combination justification of the combination drug formulation. If a sponsor pursues a combination of approved single drug therapeutics that have existing dose ranges in their approval, then the ranges should be allowable in the combinations if the combinations are eventually justifiable.

The clinical trial protocol for pursuit of efficacy data for drug combinations is very similar to that for single drug formulations. The sponsor must rationalize the experiment and outline the goals that are required to reach a decision. The measurements in combination drug experiments are basically the same as those in the single drug experiment as well. However, it is very important when dealing with combination drugs that the investigator be extremely sensitive to the need for precision in observations. Pursuit of combinations with similar claims, usually results in extremely small differences among treatment groups and strict adherence to protocol is very important. The statistical procedures to be utilized in evaluating the data should be outlined and reviewed with CVM in a pre-trial conference. Again, one can't over-emphasize the importance of CVM review and concurrence with the protocol prior to embarking upon any field trials. The need to justify the combination hinges upon the sponsor and CVM mutually agreeing upon the scientific approach and the parameters to be utilized in evaluation of the data set. Additionally, agreement must be reached on the statistical procedure to be utilized with that data set for interpretation of success or failure.

An example of an experimental design to evaluate approved products with different claims in combination is presented in Figure 2. This example outlines antibacterial X with a swine dysentery claim and anthelmintic Y with a swine ascarid claim. This combination is easily rationalized since both diseases are very prevalent within the swine population. The experimental design is a 2 X 2 factorial. Two different experiments would probably be required. In an experiment evaluating the combination and each drug in a swine dysentery disease state, one must demonstrate that the X component of the XY combination is superior to the anthelmintic Y for the treatment of swine dysentery. Similarly in a swine ascarid disease state, one must demonstrate that the Y component of the XY combination is superior to the antibacterial X for the control of swine ascarids. In this experiment, a non-medicated infected control is probably not necessary. Since these two diseases are quite different, it is anticipated that there would be large observed differences among treatment groups. Therefore, few experimental subjects would be required in each experiment to demonstrate the utility of this combination.

In Figure 3, a similar example is given for an experimental design for approved products with different claims. However, in this case both drugs proposed for the combination are active against a disease organism that is present in the same disease state, namely swine pneumonia. In this case, antibacterial X has activity against **Mycoplasma sp.** and antibacterial Y has activity against **Pasteurella sp.** Since both drugs are approved in this example, a dose response study would not be necessary and the approved fixed doses could be utilized in the 2 X 2 factorial as shown. Similar to the example in figure 2, two experiments would probably be required. It would be necessary to demonstrate that the X component of the XY combination was superior to the antibacterial Y for the therapy of mycoplasmal pneumonia in swine, and the Y component in the XY combination was superior to the antibacterial X for the therapy of pasteurella pneumonia in swine. Again, a non-medicated infected control would probably not be necessary in this experiment. However, since both drugs are active against organisms that are pathogens in the same disease state, and in both experiments swine pneumonia is the clinical disease of concern, it is anticipated that small observed differences would result in this experiment. Therefore, it is predicted that many experimental subjects would be required in each treatment group.

An experimental design that may be necessary to evaluate potential for combining two drugs with the same claim is shown in Figure 4. In this case, antibacterial X has a claim for **Staph aureus** mastitis and antibacterial Y also has a claim for **Staph aureus** mastitis. An interpretation of CVM's posture on a combination of this nature suggests that dose titration would be required since both drugs must be demonstrated to contribute to the claim. The 4 X 4 factorial as shown in Figure 4 should be the maximum experiment that would be required. Three non-zero levels of each antibacterial X and Y must be evaluated as well as all possible combinations of each level of each drug. However, as was discussed at the 1983 AAVPT

symposium on dose determinations, it was brought out many times that clinical trials are not the easiest method to identify appropriate doses because of the potential for small observed differences among treatment groups in clinical studies. In an experiment of this nature, it is possible that the combination X_1 Y_2 or the combination X_2 Y_1 could provide efficacy equivalent to either Y_3 or X_3. However, CVM's current interpretation of that hypothetical data set would not allow the combination to be justified since the single drug at higher concentration provided an equivalent result and therefore, both drugs were not necessary. An interpretation such as described is highly controversial. In this case, the decision whether or not a combination of drugs is used as opposed to a single drug should be the sponsor's decision, and not a legal one, as long as the sponsor can demonstrate that the two drugs in combination are safe both for the target animal and humans. One large experiment would be required in order to pursue a combination of this nature. Very small observed differences are likely outcomes of an experiment of this type, therefore, very many experimental subjects per treatment group would be required. This type of an experiment is one that demands precise observations on the part of the investigator and rigid protocol adherence to a greater extent than would probably be required in clinical trials evaluating a single drug.

Only some of the many possible experimental designs have been discussed. As mentioned earlier, each proposed drug combination must be approached individually and the experimental design that is utilized for the evaluation of each combination must be appraised thoroughly prior to embarking upon any clinical studies.

CONCLUSIONS

1. Each proposed drug combination is unique. Rigid adherence to regulatory guidelines may prevent availability of rational combinations to the veterinarian and/or the producer.

2. Experimental design of clinical trials for evaluating drug combinations is influenced heavily by the claim(s) desired for the combination by the sponsor as well as the need for dose determination.

3. The experimental design to evaluate combining of drugs with different claims may require only few treatment groups and small numbers of experimental subjects.

4. The experimental design to evaluate combining of drugs with similar claims usually requires many treatment groups and large numbers of experimental subjects.

Figure 1. Examples of Potential Drug Combinations

Different Label Claims

Antibacterial & Anti-inflammatory

Antibacterial & Anthelmintic

Topical Formulations

Antibacterial
Antifungal
Anti-inflammatory
Miticide

Similar Label Claims

Antibacterial & Antibacterial

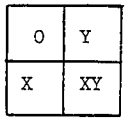
Anthelmintic & Anthelmintic

Figure 2. An Experimental Design to Evaluate a Potential Drug Combination of Two Approved Drugs with Different Claims in Different Disease Syndromes

0	Y
X	XY

0 = Non-medicated Infected Control
X = Antibacterial - Swine Dysentery Claim
Y = Anthelmintic - Swine Ascarid Claim

Figure 3. An Experimental Design to Evaluate a Potential Drug Combination of Two Approved Drugs with Different Claims in the Same Disease Syndrome.



O	Y
X	XY

O = Non-Medicated Infected Control

X = Antibacterial - Mycoplasmal Pneumonia Claim

Y = Antibacterial - Pasteurella Pneumonia Claim

Figure 4. An Experimental Design to Evaluate the Potential for Combination Justification and Identify an Effective Dose of Two Approved Drugs with the Same Claim

0	Y_1	Y_2	Y_3
X_1	X_1Y_1	X_1Y_2	X_1Y_3
X_2	X_2Y_1	X_2Y_2	X_2Y_3
X_3	X_3Y_1	X_3Y_2	X_3Y_3

0 = Non-Medicated Infected Control

X = Antibacterial - *Staph aureus* Mastitis Claim

Y = Antibacterial - *Staph aureus* Mastitis Claim