

Interface of FDA Product Decisions and Science

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The extraordinary challenges before us during and after this symposium are awesome indeed. All of us are in the unique position of balancing the complexities of melding contemporary science with laws, social policy, and public as well as private gain. These elements are in various states of change and this dynamism adds to the challenges. I suggest that perhaps the most important thing we do here may well be to faithfully consider the other person's point of view. Utilizing sound science as our cornerstone, traditions should be openly examined and perhaps reaffirmed with proper attention paid to facilitating constructive exchanges of new ideas. I am sure that all present share my desire in this regard.

The Twenty-Sixth edition of Dorlands Illustrated Medical Dictionary defines "posology" as the science of dosage or a system of dosage.¹ The word is derived from the Greek word "posos" which translates to "how much." However, the posologic aspects of a drug substance which produces a desirable result goes beyond the simplistic "how much" to include the total therapeutic strategy encompassing timing, site of action, clearance, and ultimately effectiveness and safety - all directed towards disease resolution. How often, how long, in what form, and at what site are equally important parameters for consideration.

Later in this Symposium, a fine array of talented speakers will discuss various approaches to establishing proper doses of drugs including pharmacokinetics, animal models and clinical studies. A central theme about to emerge is that there is likely more than one scientifically acceptable way to set the course of therapeutics; that is, while many roads lead to Rome, the challenge is to pick the best thoroughfare for a particular product-type always keeping in mind the benefit/risk judgements. The question of a proper dose is not isolated in and of itself for dose intelligence data and findings must regularly be balanced against toxicity.

The Bureau of Veterinary Medicine, academia and drug sponsors have utilized multiple approaches in establishing doses. I do not intend to steal anyone's thunder at this early stage of the proceedings, but a few examples of how doses have been determined and how data were evaluated by BVM may be apropos now as a starting point.

Many product approval decisions in the past 10 years have primarily relied on dose determination using a three-none-zero point strategy. The foundation for this popular dose determination approach rests in the BVM Combination Drug Policy of 1973/78.² Embodied in that document lies a requirement to establish an optimum dose. The origins of this requirement apparently stemmed from the need to construct dosing schemes with relatively high precision for combination drugs in feed, particularly for production claims to detect small, but important, drug benefits. Over the years, these scientific principles were applied to therapeutic agents in dosage forms although the response to therapeutic drugs is usually more readily discernible and perhaps engenders greater judgmental analysis.

The three non-zero point strategy encompasses a demonstration of a dose level giving less effectiveness, another providing acceptable efficacy, and a third showing no substantial improvement in effectiveness. The intent is to bracket the best dose so that the target dose level will be the middle non-zero dose in the design. While pharmacokinetic data has played a somewhat secondary role in this scheme, target animal model development that would satisfy biometrical needs has proliferated. Some excellent models have been constructed which have been validated both in the laboratory setting and verified through clinical testing. An example of this model strategy is the use of Lowe's model for induced colic and the screening of analgesics for colic pain in the horse.³ Utilizing this model, dose response curves have been established for several drugs utilizing relatively objective observations. Subsequently, the targeted doses have been examined and verified under clinical conditions.

On the other hand, several fine attempts to construct acceptable models for drugs like topical antimicrobials have not worked well. That is perhaps understandable because many disease problems are not readily amenable to models and/or the expense involved is not commensurate with the gain.

Scientific questions also creep in about the reliability of models as true predictors of the clinical disease in animals and whether model determined doses are not sometimes clinically justified by the selection of less severe clinical cases.

An important consideration with models involving anti-microbial drugs is the intensity of the infection established and the pathogenicity of the organism selected for study. In some instances we have seen the lack of establishment of expected dose responses because the pathogen was too weak to provide a severe enough disease challenge among the dose groups. Another seemingly innocent impact from an antimicrobial model approach, which did not discriminate among dose levels, involved the pharmacokinetics of the drug. The body system selected for conducting the dose determination was the same one within which the greatest elimination of an active metabolite occurred. Therefore, the lowest dose was shown to be as effective as all higher doses. While these examples of potential pitfalls should not be viewed as bars to using models, they do clearly reveal the need for careful thought and planning.

BVM approvals customarily require at least two adequate and well controlled effectiveness studies, including field (clinical) studies. The need for two studies has also stimulated extensive laboratory dose determination explorations in addition to the field studies. This statutory requirement may well have lead to a bit of scientific black boxing to construct a laboratory study of significant magnitude and impressiveness to stand on its own as one of the two controlled studies upon which to base an approval and to prepare the accompanying Freedom of Information Summary (FOI). Dose ranging finding studies on a small scale along with utilizing appropriate in-vitro data have thus been somewhat discouraged by these events.

The Bureau of Veterinary Medicine has recently recognized this trend in what some have termed overstimulation of the dose determination process. I have the pleasure of chairing a Dose Determination Group which during the past year has examined these issues carefully. The Bureau has revised its dose determination requirements for certain anthelmintic drugs for both food and non-food animals. The new approach establishes an effectiveness standard of 90% or greater for those gastrointestinal parasites in specific species for which

there is adequate support either by previous approvals or the scientific literature. The 90%+ standard applies only to adult parasitic forms since there is an inadequate history for larval forms except equine bots. A listing of the target animals and the parasites subject to this standard is available for your reference. Of course, the effectiveness data for anthelmintic claims must still include critical or controlled studies.

In practical terms of drug development, this new strategy requires only that the 90% or better effectiveness dose be established. It is no longer necessary to titrate dosages utilizing a three non-zero point protocol. The targeted dose can be tentatively established by utilizing dose range finding studies, in-vitro data, or similar means followed by a controlled or critical study to demonstrate 90% or greater effectiveness for the tentative dose level and duration of treatment. Obviously, a sponsor who elects to continue to use the three non-zero point dosage protocol will find that BVM will be glad to accept those data also. A similar approach using a blood level standard will continue to be used for systemic and sustained release sulfonamide dosage form products employing a pharmacokinetic approach to dose determination.

Consider, if you will, the following points:

1. first, the list of target animals and specific claims is not static. As progress is made and information accumulated, additions to the anthelmintic drug and claims listing will be made. Flexibility is obviously present and encouraged.
2. second, the Bureau has recognized that dose determination requirements for specific drug classes and even drugs within a class vary and thus requirements are not universal.
3. and third, By this small step on dose determination policy, a pathway is established that will facilitate discussions for appropriate scientific strategies for other groups of drugs. This Symposium is truly a major step and a useful forum for dialogue on dose issues.

Relatively few product approvals have been based on full dose determination under clinical testing conditions. Several antibacterial products have been studied in the field concentrating on varying total dose levels and regimens. This

strategy requires substantially large numbers of clinical cases and in most instances an approved drug for comparison as an active treatment control group. A major advantage of the clinical approach is that the dose is established against naturally occurring disease cases. The evaluation of these kinds of data is more complicated and requires more judgement because of the practical absence of a standardized disease intensity; that is, no two clinical cases are exactly alike. Another practical consideration is the need to define the clinical criteria for study entry and appropriate standard-ization of measurements and observation. While the clinical approach to dose determination may be fraught with scientific perils, it may well be the most informative if not the most practical strategy.

Let's change our focus for a minute towards the post-approval area of dose and effectiveness. As most of you know, the Bureau has begun a new initiative relative to the extra-label use of drugs particularly in food animals. This change is prompted by concerns over residues in food but there are also direct medical implications for health care delivery to animals. Criticisms have surfaced from veterinary practitioners against the level of effectiveness of BVM approved dosages and industry applied labeling of drugs as related to dose. Comments have generally been that dosages are too low or dosing schedules ill-timed. Most concerns surfaced have applied to anti-infective agents.

The reasons for the perceived reduction in clinical effectiveness from labeled doses and non-labeled doses are complex. One could hypothesize that scientific phenomena like pathogen resistance may be playing a role but 20 years post initial approval, host and disease pattern changes might also be involved. I can offer no concrete solutions except to endorse open communications on the subject. I do suggest that the post-symposium effort consider the issue.

A genuine thread of interest relating to my previous comments which deserves consideration is that of animal welfare concerns. Everyone involved in the drug development and evaluation process should heed the powerful and important message being sent to the research community as a whole and to veterinary medicine in particular. This message in simple terms is that all are obliged to minimize unnecessary utilization of experimental animals. Scientific experimentation and protocol writing are incomplete if questions regarding animal welfare are neglected. We are obligated ethically and otherwise to limit the adversity of

inhumane procedures and to utilize, where applicable, survival-oriented research techniques. We must see to it that appropriate safeguards are in place to preserve the well-being of test subjects. Symposia of this type can lead to the development of appropriate alternatives that fulfill both the need to advance science and to preserve the animal welfare.

I wish to conclude my remarks by making an analogy between dose determinations and my experiences as a fisherman for smallmouth bass in the upper Potomac River. This past summer my son and I enjoyed many delightful hours wading the river in pursuit of this wily sport fish. Your indulgence in my mixing pleasure with business is both respectfully requested and greatly appreciated.

I liken the determination of drug doses to wading the river. In places, there are stepping stones in the river separated and surrounded by swift current and in other areas there are complete bridges. Where complete bridges exist little in the way of assumptions and risks is required to reach the ultimate goal of safely crossing the water.

On the other hand, utilizing the stepping stones as a way of going requires assumptions and certain risks at each step. When the assumptions are sound and the risk proper, the result is that progress across the water occurs safely and effectively. However, when the assumptions are flawed and the risk too large, the result will be falling into the deep since only two individuals about 2000 years ago have successfully walked upon water.⁴ In dose determinations, let us all chart courses based upon sound scientific assumptions and conclusions so that our steps lead us securely to the side of providing needed safe and effective drugs. The challenge we face in the ensuing days is to define the rightful roles for both innovation and tradition in establishing correct dose levels and courses of therapy for new animal drugs.

Thank you.

REFERENCES

1. Friel, J.P.: Dorland's Illustrated Medical Dictionary, ed. 26. Philadelphia, Saunders, 1981, p. 1056.
2. Bureau of Veterinary Medicine: Revised Guidelines for Drug Combinations for Use in Animals, November, 1978.
3. Lowe, J.E.: Xylazine, pentazocine, meperidine, and dipyron for relief of balloon-induced colic: A double blind comparative evaluation. J. Equine Med. Surg. 2:286-291,1978.
4. The Bible: The Gospel According to Matthew, Chapter 14, Verses 22-33.

ADDENDUM

BVM Policy of June 21, 1983, Effectiveness Standards for Anthelmintic Drugs - Dose Determinations.