

REGULATORY ENVIRONMENT

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The drug approval process is a long, expensive, resource consuming effort on the part of the pioneer pharmaceutical companies. It can also be looked upon as a high risk gamble because of the potential pitfalls of course changes, industry swings and unforeseen hurdles. Time to approval for animal products is measured in years and costs are counted by millions of dollars. But for products which are approved and garner a major amount of the market share for a specific use or indication, the potential profits can be financially rewarding.

The regulatory environment for animal drugs has been impacted by numerous changes in the regulations as well as specific issues such as antimicrobial susceptibility in zoonotic pathogens of food born origins. The intent of this paper is to introduce some of the numerous regulatory issues which impact the availability of drugs with and emphasis on those drugs which would be used in reproductive management programs or for the treatment of reproductive tract diseases/conditions. While some of these issues may enhance the potential for future approvals and many in the profession are familiar with the Animal Medicinal Drug Use Clarification ACT (AMDUCA), it's a little discussed fact that extralabel use of reproductive hormones is not allowed.

AMDUCA

In the early 1980's (specifically in 1983 at the AABP Annual Conference in Oklahoma City for the author), the legality of extralabel drug use (ELDU) was brought to the profession's attention. Peripheral issues were compounding and manufacturing of unapproved products, particularly for use in food producing animals. It was apparent at that time that the Code of Federal Regulations (CFR) did not recognize ELDU and that the Compliance Policy Guidelines written by the Bureau of Veterinary Medicine (now Center for Veterinary Medicine) established policies of regulatory discretion. This regulatory discretion was not law and could be changed at any time and with probably little notice. To say the least, this was an uncomfortable feeling for those people who were made aware of it. There was concern voiced about a wide variety of products from injectable vitamins to antimicrobials. At that time, practitioner awareness of what was legal and what was illegal and what defined the gray areas was less developed than it is today.

Various descriptions exist of the chain of events leading up to the passage of AMDUCA and the resulting promulgation of regulations. One section in the proposed regulations that was unchanged in the final version, despite input from SFT, ACT, AABP and AVMA was the position on the extralabel use of reproductive hormones. Unfortunately, the bottom line is that the Center for Veterinary Medicine did not and does not feel that AMDUCA applies to the extralabel use of reproductive hormones.¹ The agency agreed that comments had, at that time, been provided which identified some important reasons for extralabel use of drugs for nontherapeutic reproductive uses. CVM feels that AMDUCA's intent was directed at treating animal illnesses. Therapeutic uses for drugs would be those directed at preventing animal pain and suffering. The conclusion of the agency was that allowing extralabel nontherapeutic use would impact drug availability issues which were/are to be addressed by the Animal Drug Availability Act of 1996.

Based upon this opinion from CVM, any extralabel use of a reproductive hormone would not be legalized by the AMDUCA regulations and therefore would be illegal. Some timely examples include would be the use of gonadotropin releasing hormone to synchronize ovulation and prostaglandins to generate an ecbolic effect in the postpartum cow. There are, no doubt, numerous other examples which would not pose a threat to either the target animal or to the human food supply but these uses are technically illegal. The AVMA's Council of Biologic and Therapeutic Agents (COBTA) has considered this issue at length with one possible solution being to ask CVM for an official policy (a Compliance Policy Guideline). Further deliberations have suggested three possible responses to such a request. One response might be that compared to the antimicrobial susceptibility and pathogen load issues the extralabel use of reproductive hormones did not warrant any resource investment, and that their stated opinion¹ remained. Another would be that such a policy would be a good idea, and it would be accomplished in short order. A third possible outcome would be that the agency would become officially aware of some of the extralabel uses and would not only remind the profession that such use was illegal but would also devote some resources to enforcement. The concern about generating this latter response prompted COBTA to reconsider approaching the agency for a policy of regulatory discretion.

The AMDUCA algorithm (appendix I) is pretty straight forward in the approach to a general interpretation of the regulations generated to enact the Act.² However, all of the considerations about class of animal, species of food animal, species of animal, and approved human drugs are not relevant to reproductive hormones. The argument that animals which do not perform reproductively and have to be sold for slaughter will suffer is not considered relevant. An additional consideration is that reproduction is considered production by the agency and extralabel use of production drugs or feed additives is considered illegal. A case in point was the agency's position on the use of oxytocin to increase milk production. An exception to the ban on extralabel feed additives will be found in the compliance policy guide "Extra-label Use of Medicated Feeds for Minor Species". But, again, this use is dictated only by circumstances which threaten the health of the animal or when suffering and death would result from failure to treat the affected animals.³

Animal Drug Availability Act of 1996

The purposes of the Animal Drug Availability Act (ADAA) were to increase the flexibility of the drug approval process, increase interaction between animal drug sponsors and FDA, create a new category of drugs and support "flexible labeling". The enhancement of the flexibility of the drug approval process has been addressed by re-defining the definition of substantial evidence of effectiveness. This would permit increased flexibility in studies required to demonstrate a new animal drug's effectiveness. The final rule gives FDA greater flexibility to make case-specific scientific determinations regarding the number and types of adequate and well-controlled studies that will provide, in an efficient manner, substantial evidence that a new animal drug is effective.

ADAA also called for greater direct interaction between animal drug sponsors and the FDA during the drug development process. This would entail a presubmission conference at the

sponsor's request and discretion in order to reach an understanding of the data needed to prove safety and efficacy.

A new category of drugs, Veterinary Feed Directive Drugs, was established to address new approvals for antibiotics in feed. To make a feed additive a prescription drug, as CVM has stated their intention to approve no new over-the-counter drugs for either parenteral or feed additive routes, would have placed significant burdens on feed manufacturing mills due to pharmacy requirements. To date, only one Veterinary Feed Directive Drug has been approved, but the concept has been accepted by the industry and the sponsors.

The concept of professional flexible labeling or flexible labeling permits a range of acceptable/recommended doses to appear on animal drug product labeling, rather than one optimum dose was also included with ADAA. This effort was the culmination of two years worth of deliberation by the Agency, the veterinary profession and the pharmaceutical industry. The concept resulted in the publication of a "strawman" label⁴ as a prototype/example of what this type of drug label might look like. Unfortunately, in early 2002, CVM published their intention to withdraw this as a model for antimicrobials. The issue of antimicrobial susceptibility has impacted the drug approval process in this and other areas.

ADAA has resulted in the development of regulations in two required areas, the definition of substantial evidence and the formalization of the presubmission communication processes between the agency and drug sponsors. Prior to ADAA, the requirements for numbers of trials repeated at separate geographic locations increased the amount and detail of data required for approvals. The current definition of "substantial evidence" now states one or more adequate and well-controlled study where it can be reasonably concluded by experts that the new animal drug will have the effect it claims. This definition is directed solely at efficacy claims while the human food and target animal safety issues are still appropriately rigorous. The concept of the presubmission conference details interaction between the agency and the sponsor prior to submission of a drug for approval. The regulation details how the conference can be requested and the procedures for the conduct of the conference.

Minor Use and Minor Species (MUMS) Initiative

In the most recent legislative session, the MUMS bill was unable to clear the final hurdle for consideration and was not attached to any larger piece of legislation. The concept, however, remains viable and enjoys a broad base of support throughout the industry, the profession, and the regulatory agencies. The focus for this legislation is to ease the approval requirements for efficacy on approval submissions for indications where the potential for usage is low and the economic return to the sponsor may not justify submission under the current guidelines. Human food safety and target animals safety would still have to be assured. The granting of "conditional approval" status would allow for a period of 5 years for the final efficacy data to be submitted.

The definition of a minor species is a matter of regulation but the concept of a minor use is a gray area. Early in the consideration of this issue, it became apparent that the veterinary profession did not have good statistics on disease incidence which increases the difficulty of

stating that a disease occurs at an incidence rate of 2 per 100,000 in the animal population, for example. The human side of the drug approval process has an “orphan” drug category for treatments of diseases which fall below a certain incidence level.

One interpretation of this gray area would suggest that developing a product for treating embryo transfer donors would address a more limited population than a drug directed at synchronizing estrus or ovulation in a specific species or class of animal. Therefore, one of the many currently used protocols for synchronizing ovulation for timed artificial insemination would be used on a population of animals too large to qualify for “minor use” status. The concept was probably intended for anesthetics and specific disease indications such as abomasal ulcers where the need for therapy was relatively infrequent.

Supplemental Claims for Approved Products

Because AMDUCA does not extend the privileges of ELDU to the use of reproductive hormones, the label indications become increasingly important. Estrus synchronization is not ovulation synchronization and treating pyometra is not administering an ecboic agent to a cow with a postpartum metritis. Supplemental label claims are a route to increasing the usefulness of a reproductive drug but there are several concerns to be faced by the drug sponsors.

The minimal studies required for adding a new claim/indication to a currently approved drug would be dose determination and clinical efficacy studies. This is assuming that the dose for the new indication is close to the currently approved dose which would reduce or eliminate the need for any further toxicity or safety studies. These reduced requirements for a supplemental label claim, by some estimations, could cost upwards of a million dollars. The drug sponsors have to be assured of a reasonable likelihood that the investment of money and resources will be a profitable decision.

One final concern for the drug sponsors would be the possibility of CVM asking to review part or all of the data on the original submission. If scientific methodology had advanced regarding residues detection limits, pharmacokinetic studies or drug metabolism and elimination or if some concerns about the original efficacy studies surfaces, the sponsor may actually be at risk of losing the original label claim. There may be some understandable hesitation on the part of the sponsors to place a major indication at risk when the supplemental indication would not increase product sales to any great degree.

Summary

The use of drugs in the treatment of conditions of the reproductive tract or in the development and implementation of reproductive management programs on an operation is an area of significant regulatory concern. AMDUCA does not legalize ELDU of reproductive hormones and legislative changes at this point in time do not seem likely or indicated. The MUMS initiative does not really address many of the needs, particularly in reproductive management programs which might have relatively broad application. The regulations promulgating ADAA in the area of substantial evidence may enhance a sponsor's ability to obtain an additional label claim, but such supplemental claims are not without cost or risk. The regulatory environment for

reproductive hormones, particularly in light of the larger issues such as antimicrobial susceptibility, may be in a holding pattern in terms of policy and future approvals.

References

1. Federal Register: November 7, 1996, 61:57731 (217) 1996.
2. 21 CFR part 530.
3. Compliance Policy Guide, Sec 615.115 Extra-label Use of Medicated Feeds for Minor Species. 4/18/2001.
4. Martinez MN, Brown SA, Copeland DD, et al. Developing a model of a professional veterinary drug label. JAVMA 209:83-91, 1996

Appendix I

EXTRALABEL DRUG USE ALGORITHM



