

Role of Veterinary Pharmacologists at the Food and Drug Administration

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I appreciate the privilege of speaking this afternoon on the need for and the role of veterinary pharmacologists at the Food and Drug Administration. My experiences at the Food and Drug Administration are limited to the Center for Veterinary Medicine so when I use the term FDA, I will be referring only to the Center for Veterinary Medicine at FDA.

I want to begin with three specific statements relevant to the topic and then attempt to provide you with information to defend those statements.

1. The core science behind the majority of decisions made at FDA is pharmacology.
2. The science base at the Center for Veterinary Medicine must be expanded to meet the needs of the future.
3. The 1990's can be the "Golden Decade" for Veterinary Pharmacology at the FDA.

Pharmacology as the Core Science at FDA

To a group such as members of this society, this statement probably seems absurd. You say, "Of course it is!" But, if one looks at the employment practices of the Center over its lifetime, a different picture emerges. The facts are that there have been and there currently are few scientists at the Center with advanced training in pharmacology. The hiring practices for scientists have been and to a large extent still are based on a concept borrowed from the human drug side of FDA, that the best person to make a judgement about a drug is a physician or a veterinarian with extensive patient care experience. While this may have served the organization well in its early days and while I recognize that some influence from that experience factor is needed, today's decisions regarding the approval and continued marketing of animal health products require considerably more expertise than is usually brought to the job by a former "patient care" practitioner. To illustrate my point that pharmacology should be the core science at FDA, I have selected three

representative positions at the Center and will summarize what the basic responsibilities of these positions entail.

First though, let me remind all of us of the overall responsibilities of the FDA Center for Veterinary Medicine. The Center has two primary responsibilities and a supporting research responsibility. The first responsibility is that of reviewing applications for marketing of animal drugs. This involves about 100 full-time positions, of which about 80 are scientists. New animal drugs or changes to existing approvals are considered on the basis of efficacy, safety to the target animal, safety to the environment, and if used in food producing animals, human food safety. With the exception of environmental safety, almost all decisions are based on evaluation of research data involving the action of the drug on a biological system or systems (pharmacodynamics) or the action of the system on the drug (pharmacokinetics). The second responsibility of the Center is surveillance of drugs approved for marketing to see that they continue to meet approved standards and are in compliance with other aspects of the Food Drug and Cosmetic Act. The group handling this responsibility includes about 80 full-time positions of which about 30 are scientists. Surveillance decisions again depend upon a fundamental knowledge of pharmacology, the most visible aspect probably being the area of adverse drug reactions. Decisions regarding compliance with existing laws are often considered as legal or technical in nature rather than scientific. I think it appropriate to point out that many compliance decisions involve determining whether a product is an animal drug or not and I would hold that a knowledge of pharmacologic principles is essential.

The third responsibility is research to support the regulatory missions of the Center. The Center devotes about 40 full-time positions to this responsibility and about 25 of those are scientists. The importance of this mission can be illustrated by

the fact that of the non-personnel funds allocated to the Center, over 50% are devoted to intramural and extramural research.

The first position I want to describe is that of a primary reviewer with limited management responsibilities. Representative of this is a position of Branch Chief of the Antimicrobial Drugs Branch in the Division of Therapeutic Drugs for Food Animals. The person in this position has six other reviewers and a secretary reporting to her. When an application for marketing or for investigations on a new antimicrobial for food animals arrives at the Center, it is this person's responsibility to see that the appropriate decisions are made. The first task is to analyze the application to see if it contains all the necessary data. Here, a knowledge of both the legal requirements and the scientific aspects are essential. The scientific aspects are those obtained in any good graduate program in pharmacology in this country followed by continued learning in the discipline. Other specialists are available for consultative assistance. For example, statisticians can be asked for opinions on the validity of the statistical methods used and the conclusions drawn from statistical probabilities. The primary reviewer, however, is responsible for the final recommendation on the validity of the data and therefore should have a working knowledge of statistical handling of biological data. In evaluating efficacy of the product a host of scientific principles can be involved but they usually fall with the two classic areas of pharmacology: pharmacodynamics and pharmacokinetics. Since products reviewed by the person in this position are for use in food producing animals, two other consulting reviews are likely: one in toxicology and one in residue evaluation. Again, the specialist will provide an opinion and a recommendation but it is up to the primary reviewer to determine that the opinions and recommendations are in context and appropriate for this particular drug. The reviewer must have a working knowledge of the science used by toxicologists and residue chemists or pharmacologists. Again, such knowledge is in the armamentarium of a veterinary pharmacologist. Lastly, the primary reviewer must synthesize all the available judgements including his or her own and the consulting reviewers and arrive at a final decision and recommendation for action by the Center Director on whether the drug can be marketed and whether it shall be classed as a prescription or over-the-counter product. Analytical, judgmental and writing skills are all involved.

The second position I want to describe is that of a reviewer in the residue evaluation branch. As we have already mentioned, this person does consulting reviews for the primary reviewers in specific areas related to human food safety aspects. Two specifics are common here. One is establishment of an acceptable tolerance for the drug in the tissues of the target animal and the other is establishment of an appropriate withdrawal time for the drug. In-depth knowledge of drug metabolism and depletion is essential for persons in these positions. Again, what type of scientific background and expertise is most appropriate for a person making these decisions from scientific data presented by the sponsor company? In the past, most of these decisions have been made by PhD organic chemists and biochemists. I would hold that a background in veterinary pharmacology with expertise in pharmacokinetics would be best. In my opinion, a mixture of chemists and veterinary pharmacologists would give the proper scientific environment for the best decisions. The last specific position I want to comment on is a scientist in the part of FDA concerned with continuing surveillance of a drug product after it has been approved. This is a very important part of FDA's responsibilities. Premarket testing, while as complete as possible, can never compare to evaluation of the drug during its actual use. Therefore, monitoring of the efficacy and safety of marketed drugs requires a high level of scientific decision making. The most visible parameter is the adverse drug reaction monitoring which relates primarily to safety, but monitoring of continuing efficacy is equally important. I suspect you are getting tired of my question, but who is the best trained person to evaluate safety and efficacy of drug products in animals? The answer again is a person who understands how drugs act on biological systems and how biological systems act on drugs, the two primary components of veterinary pharmacology.

The three examples I have used can be multiplied at least 30 times at the FDA Center for Veterinary Medicine. There are close to 100 positions there that could be filled by veterinarians with specialty scientific training in pharmacology.

Let me finish this section on pharmacology being the core science at FDA with an example of one of the many continuing special types of decisions that need to be made at the Center for Veterinary Medicine. There are always sets of these types of decision-making processes taking place at CVM. They are addressed by committees or task force

groups composed of Center employees and they vary from whether or not the guidelines for determining the Rx or OTC classification criteria should be changed to whether sulfamethazine should be considered a primary or secondary carcinogen to whether or not chemicals placed in the aqueous environment of shrimp larvae constitute new animal drugs. Most of these issues use knowledge at the cutting edge of science and most also have interfaces with regulatory law. As such, they provide a good deal of intellectual stimulation for people working at FDA. My example is the responsibility the Center had for establishing new guidelines for bioequivalence during the Center's implementation of the Generic Animal Drug and Patent Restoration Act in 1989. The intellectual challenge was to develop, based on accepted scientific principles, the guidelines by which a sponsor could prove that his generic product was bioequivalent to an already approved product. The law passed by Congress gave some general instructions but left the specifics up to the scientists at FDA. I know you can see the importance of this decision-making process and how important the science of pharmacology is to it. While I believe the FDA scientists and the outside consultants did an excellent job, I still regret that we had so few people at FDA at the time with advanced training in pharmacology to help with that challenge. I hope those of you who are academicians with graduate students will be able to help rectify that in the future.

Expansion of the Science Base at FDA

As I stated at the beginning, the science base at the FDA Center for Veterinary Medicine must be expanded. Under Dr. Gerry Guest's leadership this has begun. For the past several years, of the approximately 130 scientists employed at the Center, about one-half have been veterinarians, about 20% have been animal scientists with PhD's, about 20% have been chemists with MS or PhD degrees and about 10% have been other types of PhD's (statisticians, immunologists, physiologists, etc). Of the veterinarians, most have no specialty training. During the time I spent at FDA, there were only five veterinarians with any specialty credentials (Boards or PhD) in pharmacology or toxicology. This mix of scientific credentials has probably been quite appropriate for the decisions made in the past. But, as the products of biotechnology begin to become even more prevalent, and as other pharmaceutical research becomes more sophisticated, I believe it

necessary for the Center to expand its science base. The primary change, in my opinion, should be expansion of the veterinarians with specialty credentials in pharmacology. As veterinarians with only private practice and government experience retire, they should be replaced with veterinarians that have specialty credentials in pharmacology. If suitable candidates are not available, new DVM graduates should be employed and a graduate program developed for the employee that results in specialty credentialing. A mixture of veterinary pharmacologists with advanced training in pharmacodynamics, pharmacokinetics, clinical pharmacology and toxicology will expand the Center's science base and integrate well with its current number of animal scientists, chemists, statisticians and other scientists.

The "Golden Decade" for Veterinary Pharmacology at FDA/CVM

I have attempted to show that the core science behind the majority of decisions at the FDA is pharmacology. I have also offered my opinion that expansion of the science base at FDA should primarily be an expansion of the number of scientists holding specialty credentials in veterinary pharmacology. If this truly happens, the 1990's will be a Golden Decade at FDA. Veterinary pharmacology can make a significant impact.

But it can do so only if we all participate in the effort. We cannot shirk our own personal responsibility and leave it up to Dr. Guest and Teske and others at FDA. Each of us must find ways to assist the process through our own organizations. Those of us in academe must find ways to encourage graduate students to major in veterinary pharmacology. We must find graduate stipends for such students and we must share with them the opportunities that are present at FDA for expression of their intellectual and professional talents. Those of us in industry must also seek ways to support the scientific efforts at FDA and at the schools. And, where possible, we all should encourage the moving of scientists back and forth between academe, FDA and industry to bring about better communication and more scientific cross-fertilization of each of our organizations. There are excellent opportunities for veterinary pharmacology as a discipline to make a significant impact on the FDA of the future. The challenge is for us to find ways of helping make that happen.