

## THE REGULATION OF VETERINARY PHARMACEUTICALS AND BIOLOGICALS - QUO VADIS?

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I assume the title of my address was pre-assigned with the celebration of Easter in mind. Although a quite legitimate Latin phrase, the term Quo Vadis survives in popular parlance because of the 1895 Polish novel of that title. A bit of a book review may be in order here.

Henryk Sienkiewicz, the author, successfully revived the legend which had St. Peter fleeing Rome to avoid Nero's death sentence. The story goes that the Apostle was met on the Ostian Way by a vision of Jesus Christ. In his astonishment, Peter asked, "Quo vadis, Domine?" or "Whither goest thou, Lord?" The reply from the vision was, "To Rome to be crucified again, if you forsake my people." After a few moments of understandable reflection, Peter reversed himself and went back to the Eternal City where, according to apocryphal accounts, he was crucified upside down because of his insistence that he was not fit to be killed in the manner of his Savior.

I suspect the story has something in it for all of us regardless of our political or moral persuasion. The inclusion of "Quo Vadis" in the titles of the first three papers sends a clear message to we, the speakers: the program committee has asked us to divine the direction of veterinary pharmacology, regulation of veterinary pharmaceuticals, and of veterinary pharmacy over the next few years. In other words, "where are we going," "what is our course," and "what will be happening."

I hope there is not the implied threat of execution if our prophecies fail. The really sobering thought is that most of you will live long enough to keep score.

Let me begin with a brief historical perspective. The regulation of veterinary immunizing agents traces its statutory origins to the passage of the Virus-Serum-Toxin Act of 1913. That venerable act remains essentially unchanged to this day. It has one major defect. It allows vaccine producers to declare themselves intrastate manufacturers and thus to be exempt from regulation. Even in the face of incontrovertible evidence to the contrary, the statute does not impart adequate authority to clamp down on firms that respectfully insist on the intrastate classification. That defect makes the Act operant only for those firms that choose to be regulated and, not surprisingly, most do.

The Federal Food, Drug and Cosmetic Act, passed in 1906 and amended several times since then, allows FDA to regulate all foods, drugs, cosmetics, devices and veterinary products (including intrastate vaccines) not specifically covered by other laws. The Public Health Service Act imparts authority to regulate immunizing agents of all types. And, finally, the Supreme Court (*Grand Labs vs. Harris*, 1979) recently concurred in FDA's authority over veterinary immunizing agents.

Thus, it occasionally happens that USDA requests assistance from FDA in regulating so-called intrastate vaccine manufacturers. This arrangement is managerially unsound for several reasons: 1) two departments (Agriculture and Health and Human Services) are in effect regulating one industry; 2) veterinary

vaccine regulation, under present law, will always be a low priority within FDA because of the clearer mandate to regulate animal feeds, drugs and devices; 3) the federal government should not, in my view, interpose itself into legitimate intrastate commerce.

Current efforts on the part of USDA to modernize the Virus-Serum-Toxin Act are therefore laudable. I support those efforts. There are of course disparate points of view. The Congressional Office of Technology Assessment has reviewed the issue and has concluded that regulation of all veterinary products, including immunizing agents, should repose in FDA. I predict an eventual resolution here, but not until all sides of the issue have been aired through the law-making process.

Quo vadis, Center for Veterinary Medicine? Let's look at the major issues CVM will be dealing with between 1984-90. I think these will include: 1) illegal drug use in food animals; 2) use of drugs in racing horses and dogs; 3) the approval of bioengineered products; 4) minor species drugs; 5) the conversion from process-oriented decision-making to scientific-oriented decision-making.

#### Illegal Drug Use in Food Animals

As you all know, we are now in the ninth month of CVM's Extra-Label Use Policy initiative. Most simply put, that policy declared FDA would no longer wait until a residue occurred before taking action to protect the food supply and that extra-label use of many drugs and sales of prescription drugs without a bona fide veterinary-client-patient relationship are strictly prohibited. As you know, there has been progress. A consortium of professional and consumer groups developed a definition of the veterinarian-client-patient relationship that was professionally acceptable and legally enforceable. FDA then immediately took steps to curtail the direct distribution of prescription drugs through non-professional channels, and to stop the use of chloramphenicol in food animals altogether.

These efforts have been fruitful, but the overall problem will not be over until we are first able to marshall all the resources available to us--state regulatory officials, state boards of veterinary medicine, state veterinary medical associations and others, and secondly until we in this nation adopt a more reverent attitude towards the food we are preparing for others. The notable support this movement has already engendered from all aspects of livestock agriculture moves me to declare victory in the first instance--we will not have as many flagrant violators in our midst by the end of this decade. The second instance--the national attitudinal change may or may not occur. If it does, it will not be because of FDA. Our real role is that of regulator--law enforcer, if you will--not change agent.

The concept of responsible animal drug usage begins in the veterinary pharmacology classroom, endures the caprice of the clinical clerkship, spreads to extension service and continuing education programs, and finally comes to rest on a feedlot fence where idealism meets reality. It will not and does not occur when FDA puts a mobile prescription drug pusher out of business, because those kinds of people are criminals, the kinds of outcasts society will always spawn. It occurs when nobody wants to buy the illegal goods the pusher is selling. You may say I am building sand castles, but I ask you to join me in

believing that the men and women of this nation that grow our grain, prepare our meat and produce our milk are a special type that know full well the sacred quality of their life's work. And the last thing these people would have happen is for their products to contain substances deleterious to the health of the consuming public. But their specialty is not pharmacology or toxicology, it is food production. They look to people like you to guide them, not misguide them.

#### The Use of Drugs in Racing Horses and Dogs

More and more states are considering legalization of pari-mutuel betting. Those which enter the world of horse and/or dog racing will be greeted by a melange of state regulations that bear little resemblance from state to state. And they will probably be shocked to learn that the federal government has taken no stand on the issue. The result is a confused public, a more confused racing establishment, and a potentially abused horse and dog sub-population.

What is needed is a coherent national policy on the use of drugs in racing animals. What may be needed is a national enforcement program. I predict we will get both by 1990, and I would give 50-50 odds that a national control program will be effected within the authority of either the Drug Enforcement Program or the Horse Protection Act.

We are considering convening a meeting of appropriate state officials in order to ascertain the need for federal assistance in this area. I believe this is necessary in order to prevent the eventual need for federal intercession, an eventuality I hope we can avoid.

#### The Approval of Bioengineered Products

The first bioengineered product to be presented for review represented a jurisdictional question. There were those that argued that any such product harvested from microorganisms should be classified as a biological and therefore subject to regulation by USDA. After studying the issue, FDA and USDA concluded it was not the origin of the product but the pharmacological classification that dictates jurisdiction, i.e., if the product is an immunizing agent, USDA has regulatory authority, if it is a drug, FDA has regulatory authority.

Since that decision, there have been four similar products presented for review. In no case has there been any disagreement between FDA and USDA regarding jurisdiction.

There is a problem, however. There is every prospect that the new generation of bioengineered products will represent significant veterinary medical progress. Therefore, it is incumbent upon FDA to efficiently review these applications, with the utmost concern for safety and efficacy. Historically, when novel families of drugs come on the scene, FDA has reacted by over-reviewing and thus impeding delivery of these technologies. We are committed to doing a better job this time but we must be sure about the public health and environmental implications of these products. I would very much appreciate the opportunity to discuss these and other aspects of biotechnology with members of AAVPT.

## Minor Species Drugs

No problem has been more vexing for me or as emotionally charged as the minor species issue. As you know, we published the regulation last year which allows extrapolation of data used in the approval of drugs for major species to the approval of drugs in phylogenetically contiguous minor species. I did not expect an avalanche of approvals this year and my expectation has been correct. But this is not a problem that allows a wait-and-see approach. There are species of animals that have no drug approved for any indication and economic sub-units such as sheep and goat industries that are considerably disadvantaged by the paucity of approved drugs.

We, in the American Academy of Veterinary Pharmacology and Therapeutics, need, in my view, to go to war on this problem. CVM is attacking the situation on three fronts:

- (1) The Inter-Regional 4 Program -- Now located at Rutgers University. This effort has been instrumental in identifying the needed drugs, serving as ombudsman for the minor species drug movement, and in setting up applied research projects aimed at getting minor species drugs on the market.
- (2) The Institute for Minor Species Drug Development -- CVM shortly will be announcing the award of a major long-term contract to a research institution for the purpose of developing a basic research base which will facilitate the development of drugs in minor species. By now the world of veterinary pharmacology has a fair understanding of the innate pharmacologic mechanisms characteristic of major animal species. Not so those of small ruminants, game birds, fresh water fish, estuarine and pelagic species. The pharmacokinetic eccentricities of these species and the potential for drug residues are uncharted courses. This lack of knowledge contributes in part to the static state of minor species drug development.
- (3) Orphan Drug Development -- FDA's Office of Orphan Drugs is now considering several grants to firms or individuals wishing to develop orphan veterinary drugs -- drugs for rare animal diseases for which no drug now exists. CVM formerly referred to these compounds as minor-use drugs.

I firmly believe these efforts will make a large dent in the minor-use, minor-species problem by decade's end. I feel sure all of you here today will be called upon to provide expertise in the serious national effort now beginning. I trust and hope you will all see fit to take part.

## The Conversion to Science-Oriented Decision-Making

CVM and, indeed, all of FDA have long been managed by a rather unique system. It's best called process-oriented decision-making. "Process" here connotes the felicitous and consistent use of well-established, published procedures in arriving at decisions. In other words, an orderly set of operating guidelines based either on precedent or on policy or on both.

The beautiful part of process is its eternal consistency. The most apt definition of science, in my opinion, is that found on the internal frieze of the Library of Congress, "Science is organized knowledge." The trouble is when you get it good and organized it changes. But if you have it really organized by regulation, by guideline, or by law -- you have closed the Canon and the scientist, or purveyor of the knowledge, becomes slave to the process.

Absent process, of course, you have Elizabethan tragicomic theatrics at their worst. A coterie of philosopher - kings spring up who rule wisely and well before the completely predictable fatal flaw appears. Then science gives rise to internecine warfare which takes precedence over the essential workings of the kingdom which languish while all and sundry are either deposed, deported or decapitated.

So the trick is to have a process which can accommodate the ever-changing knowledge base. We have been talking about this at FDA for several years. I fear we have allowed our slogans of the seventies -- risk-benefit ratio, risk-risk analysis, and the transcendent decision (one that I like a great deal) -- to become our excuses for the 80's. Meanwhile archaic process lumbers on.

For years, CVM had a combination drug policy which was a "no-combination drug policy" but everyone understood the policy and we halted while science marched on. For more years than that, we have had a medicated feed policy which did not contemplate the cumulative record of safety of medicated feeds. Some of our action levels are so set in concrete these go unaddressed absent citizen petitions. There are other examples too sensitive to mention.

How do you convert from process-oriented decision-making to science-oriented decision-making? You bring in the outside world and shed light in the monastery. You create an advisory committee even if it takes you years and you faithfully integrate it into the policy-making tree of the Center. You appoint consumers, practicing veterinarians and practicing scientists; moreover, you make certain that industry, the legal profession, academia, as well as the consuming public are represented and that those who are asked to serve are at the height of their powers intellectually, capable of operating on the cutting edge of science.

Then you operate your Center of Veterinary Medicine this way. You have Councils consisting of the Branch Chiefs, Division Directors, Deputy Associate Directors, and chaired by the Associate Director for each office -- Research (shortly to be re-named Science); Scientific Evaluation; Surveillance and Compliance; Management and Operations. And you have a CVM Council consisting of the Center's Division Directors, Deputy Associate Directors, Associate Directors, Deputy Director and chaired by the Director. Then, you have all internal Councils meet once per week and the external Advisory Committee meet quarterly.

Next you develop policy and review policy in the following ways: 1) the Advisory Committee will review all proposed policy changes that emanate from the CVM Council and recommend other policy changes to the CVM Council as may be appropriate; 2) the CVM Council will review the policy changes recommended by the Advisory Committee; 3) the Advisory Committee meets with the CVM Council quarterly; 4) the Director of CVM retains veto power over any and all policy decisions in order to be both consistent with delegation of authority and in

order to be the responsible administrative officer of the Center; 5) the Director and Deputy Director of CVM shepherd all Councils so as to ensure the proper functioning of a science-oriented decision-making process.

After all that, you become Solonic in wisdom and Solonic in travel habits. You also pray you never have to break a tie or use a veto.

All of you should visit or re-visit the Library of Congress the next time you are in Washington. Read the inscriptions of the friezes. Revel in your nation. It works. Take in the sagacity of the ages. It also works. Think about the revealed definition of science, "Science is organized knowledge." Reflect on those who organized our knowledge for us: Alexandre Liautard with his 1864 Vade Mecum, which I actually saw used in the 1940's; A. G. Milks with the many editions of 1911 Materia Medica, which I saw used in Edinburgh, Scotland in 1970; L. Meyer Jones' 1954 Veterinary Pharmacology and Therapeutics which I myself used this morning. It is a historical fact that all these men meandered through the Library of Congress. In addition to the "Science" aphorism, I bet they also took the time to read its companion quotation, "Who reaches lower than the stars.....reaches too low."