The State of CVM

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Despite being the smallest of the Food and Drug Administration's (FDA) regulatory centers, the Center for Veterinary Medicine (CVM) nonetheless must confront and resolve all of the bedeviling issues that the other FDA Centers face, and a few that are unique to animal and animal product regulation. The combination of regulatory complexity and scarcity of resources results in a mixed "report card" from the standpoint of any of the stakeholders in the activities entrusted to CVM. What follows is an attempt to assess how various stakeholders may view CVM's performance, rather than an "insider" assessment.

Regulation of New Animal Drugs

According to an Animal Health Institute survey of its member companies using data for the years 1998 to 2000, CVM is facing unprecedented delays in processing new animal drug applications (NADAs). The survey states that 88% of original new animal drug applications, 63% of administrative new animal drug applications, and 22% of supplemental new animal drug applications are overdue. The Federal Food, Drug, and Cosmetic Act (FDCA) requires CVM to make a decision on new animal drug applications within 180 days.1 The survey concludes that CVM's review of NADAs "may take an additional 1.5 years beyond what is normally required to complete the animal drug review process." According to the March/April 2000 issue of the FDA Veterinarian, in 1999, CVM approved five NADAs for new chemical entities. According to the March/April 2001 issue, during 2000, that number was three. Approving new animal drugs was not included on CVM's list of its top three priorities posted on the Center's website in May 2001.

CVM did, however, list antibiotic resistance as one of its top three priorities. The theory is that the use of antibiotics in animals may foster antibiotic resistance in humans with respect to foodborne illness. In the January 6, 1999 Federal Register (64 Fed. Reg. 887), CVM announced the availability of a framework document outlining how it would deal with antibiotic resistance issues. That document proposed to classify drugs according to their relative importance in human medicine and discussed the establishment of thresholds of resistance to determine whether an approved drug should be restricted or removed from the market.

In 2000, CVM published a risk assessment on the human health impact of fluoroquinolone-resistant campylobacter associated with the consumption of chicken. CVM cites as the major strengths of its risk assessment model its mathematical simplicity and the ease with which

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1 "Administrative NADAs" are those filed after the completion of all of the substantive reviews under a phased submission of an NADA; they are supposed to move more quickly as all substantive issues have been resolved.
it can be updated as new data become available. Critics of the document relate that CVM's process fails to follow the National Academy of Science's model for risk assessments that has been followed by FDA's Center for Food Safety and Applied Nutrition and the U.S. Department of Agriculture's (USDA's) Food Safety Inspection Service, resulting in a model that produces biased results. Despite these criticisms, CVM has announced plans to pursue another risk assessment on the public health impact of streptogramin-resistance in human infections of Enterococcus faecium attributable to the use of strepto-gramins in food-producing animals.

In the October 31, 2000 Federal Register (65 Fed. Reg. 64954), CVM published a Notice of Opportunity for Hearing (NOOH) proposing to withdraw approval of the NADA for use of the fluoroquinolone antimicrobial enrofloxacin in poultry, based in part on its risk assessment and a determination that fluoroquinolone use in poultry is temporally and functionally related to fluoroquinolone-resistant campylobacter infections in humans. Critics of the NOOH attack numerous aspects of the underlying science and the public policy of the Center's action, contending that it is based on an inappropriate risk assessment and a temporal association that is contrary to available data. At the time this article goes to press, FDA has not yet announced whether it will grant a hearing in this case.

In sum, CVM is pulled in different directions by different stakeholders, with applicants criticizing the delays in reviews and approvals, while consumer groups complain of the lack of aggressive action to restrict or prevent antibiotic use in food producing animals.

**Regulation of Animal Feed**

Another of CVM's top three priorities is the prevention of Bovine Spongiform Encephalopathy (BSE — mad cow disease). For several years, CVM has been involved in the issue of monitoring for BSE. That activity appears to have been intensified in the early part of this year. In response to growing concerns about BSE, on December 4, 2000, the European Union imposed an across-the-board six-month ban on the feeding of processed animal protein to farmed animals, to go into effect on January 1, 2001. On December 7, 2000, USDA implemented a ban on the importation of rendered animal protein, regardless of species, from Europe. CVM published its own document on January 20, 2001 in the form of Import Alert No. 99-25, which announced that CVM would detain without physical examination animal feeds and certain other products of animal origin.

FDA regulations banning the feeding of a variety of mammalian proteins to cattle went into effect in the United States in 1997, well in advance of more recent EU actions, but are not as broad, being limited to feeding of cattle. These regulations are designed to prevent the development of BSE in the United States, which is believed to have originated from certain practices in the U.K. of feeding ruminant proteins to cattle. The regulations carry detailed requirements for the handling of animal feeds that contain those mammalian proteins that cannot be fed to ruminants, including labeling and paperwork requirements and procedures for preventing commingling of the prohibited mammalian proteins with feeds that can be fed to ruminants.

CVM set as its goal "100% compliance" with the regulations, a goal which both producer and consumer groups supported. Therefore, in conjunction with USDA and state animal feed regulators, CVM began a series of inspections in early 1998 of renderers and licensed and unlicensed feed mills to educate these entities about the requirements of the regulations and
ensure appropriate compliance. Dr. Stephen F. Sundlof, Director of CVM, has stated that the Center expected an approximately 25% non-compliance rate on first-time inspections, primarily because not all entities would have been informed of the regulation and its requirements.

Results published on January 10, 2001 on CVM’s website show that CVM, USDA and the states had conducted a total of 9,947 inspections, and FDA field offices were assigned to re-inspect 700 firms found not to be in full compliance with the rule but which had committed to implementing the regulation. By April 2001, over 10,000 inspections had been conducted, including 834 re-inspections. CVM projects that the inspections will be completed by September 30, 2001.

**Regulation of Nutritional Supplements for Animals**

Historically, CVM has taken the position that provisions for "dietary supplements" added to the Act by the Dietary Supplement Health and Education Act of 1994 (DSHEA) do not apply to animal products. In 1998, Dr. Sundlof told the Pet Food Institute (PFI) that depending upon the claim made for the product, CVM considers "nutraceuticals" to be either drugs or food additives. FDA deems these products to be drugs if either they are intended to treat or prevent a disease or they have a structure/function claim and are not a food article. Dr. Sundlof told PFI that as then-labeled, CVM considered most of these products to be drugs but that CVM would exercise regulatory discretion with respect to these products, provided that manufacturers assure the safety of the product. Manufacturers could do so, for example, through a Feed Ingredient definition approved by the Association of American Feed Control Officials (AAFCO), which is the association of state animal feed regulators. Dr. Sundlof also recommends that manufacturers guarantee those ingredients as necessary to support content claims, attach disclaimers as appropriate that the ingredient is not recognized as an essential nutrient on the AAFCO Food Nutrient Profiles, and not include a "Supplement Facts" box or the disclaimers that appear on human dietary supplement labels.

CVM participated in an attempt by AAFCO to create a framework for regulation of un-approved dietary ingredients in animal feed that states and industry could use as guidance. In 1999, AAFCO created the Novel Ingredients Regulatory Framework Task Force, which was charged by the AAFCO Board of Directors with drafting such a framework. CVM representatives were members of the task force. Although the task force made significant efforts toward drafting a framework document, it was ultimately disbanded in late 2000 before the framework document could be completed. AAFCO has replaced the task force with the Enforcement Strategy for Marketed Ingredients Work Group. At this point, therefore, these feed ingredients continue to be regulated on an individual state basis. Neither the states, product producers, nor CVM is really satisfied with the current approach, but from the standpoint of CVM's priorities and resources, it appears to be the best that can be achieved at the present time.

**Regulation of Transgenic Animals**

CVM has announced that it intends to be the federal government entity that will regulate transgenic animals. Indeed, the last of CVM's top three priorities posted on its website in May 2001 is ensuring the safety of food derived from genetically modified animals. Dr. Sundlof has announced that all bioengineered animals can be viewed as containing new animal drugs because the bioengineering "alters the structure/function of the animals," which is a key part of the definition of a "drug." Dr. Sundlof points out that CVM must regulate the animals because the
animals themselves could enter the food chain. Alternatively, if the animal is genetically modified to produce a particular product, the residue from that product, such as meat or egg derivatives remaining after removal of the product, could enter the food chain. Although CVM does not appear to have settled on the precise manner of regulation for each potential product of transgenic animals, it appears that the level and mechanics of the regulation may be tailored to be consistent with the end product.

The use of the new animal drug provisions of the FDCA, particularly given the resource and time frame issues outlined earlier, could potentially lead to a much slower review by CVM than is accomplished by its sister Center for Food Safety and Applied Nutrition (CFSAN) in reviewing plant biotechnology. Unlike CVM's use of a licensing mechanism, CFSAN has carefully avoided characterizing modified proteins in plant biotechnology as "food additives" which would require licensing, despite the urging of many consumer groups. CFSAN has published its proposal for a formal "notification" process. CVM has yet to publish its proposal on the scope and form of regulation.

Conclusion

This overview skims the surface of CVM's activities and obligations. It does not touch, for example, on the growing burden of applications for drugs for companion animals, or the potential for new legislative relief in the area of "orphan drug"-like procedures for minor uses and minor species (captured by the acronym "MUMS"). But in these four areas of important and controversial regulation — new animal drug approvals, protection against the introduction of BSE in feed, the rational regulation of dietary supplements for "animals other than man," and a forward-looking regulatory system for transgenic animals — CVM has shown a bewildering mix of focused activity (BSE concerns), unclear allocation of resources (NADA approvals for transgenic animals), and less than benign neglect (dietary supplements). Congress increasingly gives FDA money for specific assignments within a recognized field of activity; the Center involved has no discretion in altering the priorities for using those funds. It may be time for Congress to signal how CVM's funds should be used among its competing demands rather than, in effect, underfunding everything.

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