

The FDA Veterinary Medicine Advisory Committee (VMAC) met January 22-24, 2002 to discuss two issues: 1) establishment of import tolerance for nonapproved drugs and 2) whether pathogen load studies are necessary for antimicrobial approvals. The FDA typically asked multiple specific questions of the panel. The following is offered as my synopsis of those issues and the general VMAC responses. Note that the following are not necessarily the views of the FDA.

1. Import tolerances. As part of the Animal Drug Availability Act of 1996 it was specified by Congress that the FDA should establish tolerances to allow importation of products containing residues of drugs not approved for use in food animals in the U.S., provided evidence existed to establish said residues as reasonably safe. The FDA was seeking advice on what methods should be used to establish those tolerances. In that regard, two main approaches were reviewed:
 - a) It would usually be possible to establish tolerances by review of toxicity studies in a manner currently employed by FDA for domestic drug approvals. The committee termed this the Food Safety approach.
 - b) When setting tolerances some countries take into account “Good Agricultural Practices”. The tolerance value in such cases is a reflection how the drug is used. Exceeding that value implies that the drug is being used in an improper manner. Typically tolerance values set in this manner are lower than those set using the Food Safety approach. As some countries have already set their tolerances on this basis, and since these values are lower (more conservative) than that of the food safety approach, the argument was made that the US should adopt this approach in the interest of having only one tolerance value for that drug-product combination (international harmonization of import tolerances). The committee termed this the Good Agricultural Practices approach
- It was the overwhelming opinion of the VMAC that import tolerances should be based on the Food Safety approach similar to that currently employed by the FDA. While the concept of international harmonization taking into account Good Agricultural Practices is laudable, the difficulties in defining those practices as well as the prospect of facing dual tolerance values should a foreign drug eventually seek domestic approval made this latter approach inadvisable. The committee noted that some form of assurance that the drug producing these residues is manufactured under GMP-like conditions should be required.

Other issues dealing with import tolerances:

- Tolerances are typically set for sponsor specific products and not for a the chemical entity. The FDA asked if there were methods whereby residues could be identified as associated with a specific product. The VMAC could think of no practical methodology to accomplish this task.
- The FDA sought guidance as to when the public should be made aware that an import tolerance was under consideration. The VMAC felt that an initial review by the FDA was first in order to determine the completeness of the submission package. If said package was deemed adequate to determine a tolerance the public should be made aware that establishment of an import tolerance was under consideration. This public notification should occur via the Federal Register, the CVM web site, and other avenues as may be appropriate. That notification

should be in a timely manner to allow for adequate public feedback and consideration of public concerns prior to ruling on the import tolerance.

- The FDA was seeking information on whether setting of these import tolerances could have a significant environmental impact that might disallow an exclusion relative to the National Environmental Policy Act. The VMAC could think of no instances relative to residues within animal products that would have a significant environmental impact.

2. Pathogen load studies. FDA has required by regulation (21 CFR 558.15) that “pathogen load” studies (more specifically, *Salmonella* shedding studies) for any antibiotic being used for subtherapeutic purposes in animal feeds (use beyond 14 days). These studies were to address the issue of whether subtherapeutic administration of the drug led to an increased number of *Salmonella* in the GI tract of the target species (and hence an increased risk of carcass contamination at slaughter). In addition, the “558.15 studies” attempted to evaluate whether such drug use led to increased resistance to antimicrobials. The FDA was seeking advice as to whether the pathogen load studies in particular should continue to be applied to subtherapeutic use applications and whether they should be expanded to include therapeutic use applications.

Presentations by a variety of speakers reviewed the benefits and flaws of pathogen load studies. An outside consulting group, on behalf of the FDA, also conducted a literature review and those results were provided. Major limitations of the 558.15 study design were apparent and included: age groups and husbandry practices not representative of drug use conditions, inordinately high bacterial challenges, not studying the effect of the drug withdrawal time frame where pathogen numbers might reduce or stabilize, and an inability to accurately quantify *Salmonella* numbers based on present technology. The literature review and the review of 558.15 studies failed to show consistent evidence of antimicrobial use causing increasing pathogen numbers and in fact more commonly showed pathogen number reductions. No evidence of increased resistance due to drug use was found in any of these studies.

- While the concept of requiring pathogen load studies for drug approval may seem reasonable in theory, the VMAC felt that as presently designed pathogen load studies provided no consistent value in protecting the public health. Several members commented that resources would be better spent relative to antimicrobial resistance rather than pathogen load determinations. It was the majority opinion (ten members) of the VMAC that such studies should be discontinued for subtherapeutic drug approval purposes and that they not be incorporated into the therapeutic drug approval process. Though acknowledging the limitations of the present system, two members offered a dissenting opinion stating that they felt pathogen load studies should be continued in some form.

Respectfully submitted

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