



AMERICAN VETERINARY MEDICAL ASSOCIATION

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March 6, 2002

Docket No. 01N-0284
Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: DOCKET NUMBER 01N-0284, Advance Notice of Proposed Rulemaking – Import Tolerances

Dear Sir or Madam:

The American Veterinary Medical Association, on behalf of its 67,000 members comprising 85% of the active veterinarians in the United States, wishes to comment on issues related to the import tolerances provision in Section 4 of the Animal Drug Availability Act of 1996 (ADAA) which authorized FDA to establish drug residue tolerances (import tolerances) for imported food products of animal origin for drugs that are used in other countries, but are unapproved in the United States.

The objective of the AVMA is to advance the science and art of veterinary medicine, including its relationship to public health, biological science, and agriculture. The Association provides a forum for the discussion of issues of importance to the veterinary profession and for the development of official positions in related areas. The Association is therefore the authorized voice for the profession in presenting its views to government, academia, agriculture industry, animal owners, the media, and other concerned bodies.

The AVMA has historically been a strong supporter of the ADAA and food safety, including the establishment of drug residue tolerance levels in food products, based on public health evaluations. We offer the following for consideration on the issues, as requested in the ANPRM:

Issue 1

FDA sets tolerances based upon the ADI and the relationship between the marker analyte and the total residue. To establish the tolerance, FDA considers conditions of use (including formulation, dose, and route of administration) and manufacturing features (including drug potency and purity). Regulatory agencies outside of the United States and international organizations may use different or additional factors to establish maximum residue levels (MRLs). The factors used by

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these regulatory agencies may include different edible tissue consumption factors or animal husbandry standards such as good agricultural practices. The effect of considering these factors may be a different tolerance value than the value established only on the basis of the human food safety data (as presented in section I B of the ANPRM).

Question: There are different approaches that FDA could use to find a safe import tolerance. FDA could look at toxicity and residue data and build in a conservative safety factor. Alternatively, FDA could also review conditions of use such as good agricultural practices, route of administration, and dose, which may result in a different safety factor or factors. Additionally, FDA could consider manufacturing information such as that required for a domestic application, which also could result in a different safety factor or factors. Which approach is preferable?

Response: This question apparently focuses solely on the determination of a "safety factor" which is understood to be the number that a no-effect level (NOEL) dose is divided by to calculate an acceptable daily intake (ADI) and subsequently the safe concentration of parent drug and metabolites in edible tissues. The safety factor is typically selected as 100 or 1,000. The most preferable approach to this issue is to select a safety factor identical to that imposed on the manufacture, sale and use of drugs for domestic food animals. This would have the dual beneficial effect of reassuring consumers that imported food supplies are equivalent to domestic food animal supplies and promoting international harmonization of food animal drug approval requirements. It does not seem advisable for FDA to consider adjustment of safety factors based on "typical" agricultural or drug administration practices in the international market.

Issue 2

The tolerance established by FDA for a new animal drug approved under section 512(b)(1) of the act is based on data submitted by the sponsor. These data are owned by the drug sponsor (pharmaceutical company, producer organization, etc.) that paid for the study and is accountable for the quality of the research. Each subsequent sponsor seeking approval of the drug under section 512(b)(1) of the act must submit similar human food safety data as required to support the tolerance for their product. Each new animal drug tolerance is established for each drug product, rather than for the drug substance/active ingredient. However, the ADAA allows for data for an import tolerance to include "data submitted by the drug manufacturer to appropriate regulatory authorities in any country where the new animal drug is lawfully used or data available from a relevant international organization* * *." Any country wanting its producers to become eligible to export to the United States, could be a sponsor of an import tolerance.

Question: Only the drug marker residue for the drug substance, not the product formulation or the sponsor of the import tolerance, can be determined by the type of analytical method that is typically used to assay imports. Are there analytical techniques or other approaches that would allow us to determine whether a residue is due to use of the drug product for which the tolerance is approved?

Response: This question seeks technical information on alternative technical approaches to residue detection. It is possible that there are alternative chemical or immunologic techniques that are sufficiently robust to meet the demands of import food testing for specific drugs and tissues. However, it will be an immense undertaking to establish and validate these tests for all drugs and all food products. It is much more preferable to interpret the ADAA statement cited in

this issue in its narrowest sense. In such a case, these data would be required to conform to FDA or CODEX tolerance setting procedures. The objective of this interpretation must be consumer safety and international harmonization.

Issue 3

FDA is considering how it should inform the public of the import tolerance process while also ensuring that FDA does not disclose trade secrets and confidential commercial information.

Questions:

(a) Should FDA disclose to the public that it is considering an import tolerance for a new animal drug?

Response: The response to this question is divided into three conditions. Firstly, if the import tolerance request is from a sponsor who is also seeking FDA review of the drug as a NADA, then the FDA should not disclose to the public that this is under consideration. This will protect trade secrets and confidential commercial information. Secondly, if the import tolerance request is from any other organization then the FDA should disclose to the public that this request is under consideration. Thirdly, the FDA should disclose the establishment of an import tolerance regardless of the submitting entity.

(b) If so, when (e.g. upon request, upon filing)?

Response: Under the second condition addressed above (Issue 3 (a)), disclosure should be upon submission of adequate technical information, and this is understood to be equivalent to "upon filing" in this question.

(c) How should FDA do so (e.g., Federal Register, Internet)?

Response: Disclosure should be through the Internet using the FDA CVM website and through the Federal Register.

(d) How much detail should FDA provide, keeping in mind that FDA cannot disclose trade secrets or confidential commercial information?

Response: FDA should provide the identity of the drug, the proposed species and target tissue. The level of detail should be consistent with the FOIA data released for domestic NADAs.

Issue 4

FDA is considering amending the regulations at 21 CFR 25.33 to allow a categorical exclusion for import tolerances under the National Environmental Policy Act, if there is information that shows that establishing import tolerances does not have a significant effect on the environment. FDA is seeking information on whether import tolerances will have a significant effect on the environment.

Response: FDA should seek such a categorical exclusion. Environmental policy regarding drug use should be the prerogative of the producing country or superceding international treaty. The objective of the import tolerance is to ensure consumer safety.

Issue 5

Please comment on any other aspects of import tolerances you wish to raise.

Response: FDA should seek to ensure that the primary process for requesting and submitting data for the determination of import tolerances is through the sponsorship of a drug manufacturer that meets GMP requirements. In particular, it will be critical to ensure that drugs used in animal production are manufactured according to a purity, potency and stability equivalent to standards maintained by manufacturers of drugs for domestic food animal use. Failure to meet these standards renders the establishment of an import tolerance potentially meaningless. This is because an acceptable level of a marker analyte in a target tissue will have little relevance if the parent drug is not manufactured to sufficient standards. Additionally, use of other tests will also provide potentially meaningless results if manufacturing conditions are inconsistent.

Additionally we fully expect that the FDA CVM will not establish an import tolerance for a drug banned in the United States for use in food animals, even if the residue level is undetectable. Within the United States, the FDA has banned six drugs that were previously approved for food animal use but were determined to present an unacceptable risk to US consumers. It is important to note that the FDA had the opportunity to establish a “zero tolerance” level instead of banning the drugs but chose instead to ban use of the drugs in food animals. Some of the drugs demonstrated potential mutagenic or carcinogenic effects, but one (chloramphenicol) was banned because of the possibility of aplastic anemia that appears to be non-dose related. The other banned drugs are diethylstilbesterol, dimetridazole, iponidazole, furazolidine and nitrofurazone. The FDA, in cooperation with the USDA, needs to ensure that these six drugs are not used in food animals, from which food products are imported by into the United States.

Sincerely,



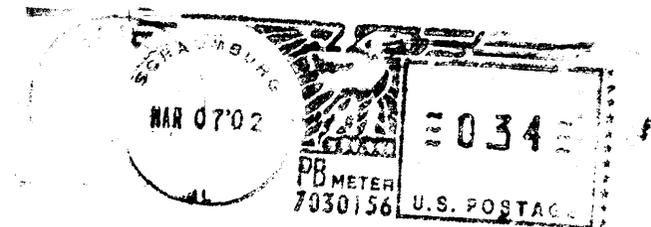
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186th AVMA Annual Convention
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