

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 500

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[Docket No. 01N-0284]

RIN 0910-AB71

**Import Tolerances**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Advance notice of proposed rulemaking.

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**SUMMARY:** The Food and Drug Administration (FDA) (we, the agency) is soliciting comment on issues related to the implementation of the import tolerances provision in section 4 of the Animal Drug Availability Act of 1996 (ADAA). The ADAA authorizes FDA to establish drug residue tolerances (import tolerances) for imported food products of animal origin for drugs that are used in other countries, but that are unapproved new animal drugs in the United States. Food products of animal origin that are in compliance with the import tolerance will not be considered adulterated under the Federal Food, Drug, and Cosmetic Act (the act) and may be imported into the United States. We plan to propose a regulation for establishing import tolerances. We plan to hold a public meeting on import tolerances during the comment period for this advance notice of proposed rulemaking (ANPRM) and intend to consider the comments made at the meeting and in response to this ANPRM in writing the proposed regulation. We also will work with the Food Safety Inspection Service of the United States Department of Agriculture and other Federal agencies in the development of the proposed regulation.

**DATES:** Submit written or electronic comments by *[insert date 120 days after date of publication in the Federal Register]*.

**ADDRESSES:** Submit written or electronic comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

**FOR FURTHER INFORMATION CONTACT:** Frances Pell, Center for Veterinary Medicine (HFV-235), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-827-0188, e-mail: [fpell@cvm.fda.gov](mailto:fpell@cvm.fda.gov).

**SUPPLEMENTARY INFORMATION:**

**I. Background on Import Tolerances**

*A. Import Tolerances—Legislative History and ADAA*

The President signed the ADAA into law on October 9, 1996. Section 4 of the ADAA concerns import tolerances and amends section 512(a) of the act (21 U.S.C. 360b(a)) by adding the following new paragraph at the end:

(6) For purposes of section [402(a)(2)(C)(ii)], a use or intended use of a new animal drug shall not be deemed unsafe under this section if the Secretary establishes a tolerance for such drug and any edible portion of any animal imported into the United States does not contain residues exceeding such tolerance. In establishing such tolerance, the Secretary shall rely on data sufficient to demonstrate that a proposed tolerance is safe based on similar food safety criteria used by the Secretary to establish tolerances for applications for new animal drugs filed under subsection (b)(1). The Secretary may consider and rely on data submitted by the drug manufacturer, including data submitted to appropriate regulatory authorities in any country where the new animal drug is lawfully used or data available from a relevant international organization, to the extent such data are not inconsistent with the criteria used by the Secretary to establish a tolerance for applications for new animal drugs filed under subsection (b)(1). For purposes of this paragraph, "relevant international organization" means the Codex Alimentarius Commission or other international organization deemed appropriate by the Secretary. The Secretary may, under procedures specified by regulation, revoke a tolerance established under this paragraph if information demonstrates

that the use of the new animal drug under actual use conditions results in food being imported into the United States with residues exceeding the tolerance or if scientific evidence shows the tolerance to be unsafe.

The legislative history notes that "the bill authorizes FDA to establish import tolerances for new animal drugs not approved in the United States" and that a September 20, 1996, letter from the Director, United States Congress, Congressional Budget Office (CBO), to the Chairman, Committee on Commerce, includes a statement that CBO expects that the Secretary of Health and Human Services (the Secretary) would not set standards for these tolerances that are significantly different from current practice. H. Rept. 104-823 further clarifies the intention of section 4 of the ADAA by stating that the section authorizes FDA to establish import tolerances by "using criteria similar to those that it would apply in reviewing the human food safety aspects of an animal drug for which approval is sought in the United States." In addition, the report states that FDA may rely on data generated by the drug manufacturer or on data from a relevant international organization such as the Codex Alimentarius Commission. The report further states that section 4 of the ADAA furthers international harmonization of regulatory requirements.

It is currently unlawful to import animal-derived food that contains residues of a drug that is not approved in the United States, unless the Secretary has established an import tolerance for that drug and the residue does not exceed that tolerance. Any amount of residue from a drug not approved in the United States and for which no import tolerance exists, even a level of residue considered safe by the exporting country, would cause the food to be adulterated under section 402(a)(1)(C)(ii) of the act (21 U.S.C. 342(a)(1)(C)(ii)), and denied entry into the United States under section 801(a)(3) of the act (21 U.S.C. 381(a)(3)). It is also unlawful to import animal-derived food that contains residues of a drug approved in the United States, if the residues are present at levels above the established tolerance.

Foreign drug sponsors may choose not to seek full approval in the United States for several reasons. It may be difficult for foreign drug sponsors to seek full approval in the United States,

in part because the comprehensive nature of the approval requirements in the United States may require a foreign sponsor to perform studies in the United States that are difficult to arrange from outside the United States. In addition, for some drugs there is little incentive for a drug sponsor to obtain approval of the drug for use in the United States because the drug is used to treat animal disease that does not occur in the United States. In this case, the U. S. target animal safety and efficacy components of the NADA would not be relevant.

Some exporting countries have many more animal drugs approved for use in some species than are currently approved for those species in the United States. Some of these drugs might qualify for approval in the United States, if a drug sponsor were willing to invest in the research studies needed to support approval. Some of these drugs may not be easily approved in the United States, because drug sponsors may not be able to meet one or more requirements of the NADA (21 U.S.C. 360b(b)).

#### *B. Human Food Safety Requirements for NADAs in the United States*

The human food safety evaluation of an NADA is predicated on the assumption that the drug product in question will be manufactured consistently from one batch to the next to the same standards of purity, strength, and identity as the product used to generate the human food safety data. The evaluation is also based on the particular conditions of use in the food-producing animal as proposed in the NADA. The human food safety data for an NADA typically include, but are not necessarily limited, to the following:

1. **Threshold Assessment**—The sponsor generally provides data that allow the agency to conduct a threshold assessment to determine the potential of the new animal drug to cause cancer. The data typically include the results of a battery of genetic toxicity studies, the oral toxicity studies discussed below, and carcinogenicity information regarding structurally similar chemicals in published or proprietary literature.

2. **Oral Toxicity Data**—The sponsor generally provides data that allow the agency to assess the oral toxicity of the new animal drug in the diet. The data are typically generated through

a 90-day rodent and nonrodent mammalian oral toxicity study, a multigeneration rat reproduction study, and a rodent teratology study. The no-effect level dose from the most relevant study divided by a safety factor (typically 100 or 1,000) is used to calculate an acceptable daily intake (ADI) for the animal drug in the human diet. Once the ADI is established, safe concentrations are calculated for total residues of the drug (the parent drug and all metabolites) in edible tissue.

3. Total Residue and Metabolism Data—Total residue depletion and metabolism data are typically generated in studies conducted with a stable radiolabel of the parent drug. The total residue studies provide data on the concentration of the total residues of the drug in the edible tissues and changes in that concentration over time from the cessation of treatment. The metabolism studies are used to determine the nature and disposition of the residues in the edible tissues of the target animal.

4. Target Tissue Determinations—Total residue and metabolism data are used to determine an appropriate target tissue which will serve as an index of the safety of all edible tissues in the target animal. The residues of a drug typically deplete at different rates for different edible tissues. The target tissue is usually the edible tissue that takes the longest to deplete, but other factors may also be considered when selecting the target tissue. The target tissue is selected such that when the concentration of drug residues is safe for consumption in the target tissue, all other edible tissue is also safe for consumption.

5. Marker Analyte Determination—A marker analyte is determined to serve as a measurable index of the total residues of the drug in the target tissue. The marker analyte may be the parent drug, a metabolite of the parent, or a known combination of metabolites.

6. Determinative and Confirmatory Regulatory Method—The sponsor generally provides a two part (determinative and confirmatory) analytical regulatory method to determine the concentration of the marker residue in the target tissue upon which to base the tolerance (see below). The regulatory method is also used in establishing the withdrawal time and in assuring the safety of food animals treated with the approved new animal drug.

7. Tolerance—A tolerance is established based upon the relationship between the concentration of the marker analyte (measured by the determinative method) and the concentration of total residues of the drug (measured by radiolabel method) at the safe concentration. The concentration of the marker analyte in the target tissue, as measured by the regulatory method, which corresponds to the safe concentration for total residues of the drug in the target tissue, is defined as the tolerance.

8. Withdrawal Study—The sponsor generally provides a withdrawal study (or depletion study) to determine the depletion time necessary from the cessation of treatment of the labeled target animal species at the maximum labeled dose and duration under normal conditions of use to the time when the marker residues in the target tissue are below the tolerance for that drug as measured by the regulatory method.

The human food safety criteria listed above are provided for the information of the reader preparing comments in response to this ANPRM. Some of these criteria would have to be modified for establishing import tolerances. For example, whole animals usually would not be imported into the United States. Therefore, the target tissue for an import tolerance would be the type of tissue that is imported into the United States. A withdrawal study is an example of a study for the approval of an NADA for use of the drug in the United States that would not be necessary for establishing an import tolerance because data from the withdrawal study are not involved in the tolerance calculation. Other criteria, such as the requirement for the sponsor to submit a regulatory method, would remain the same.

## **II. Agency Request for Information**

FDA is soliciting comment on all aspects of import tolerances and specifically on the following issues:

Issue 1: We set tolerances based upon the ADI and the relationship between the marker analyte and the total residue. To establish the tolerance, we consider 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 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 above.

Question: There are different approaches that we could use to find a safe import tolerance. We could look at toxicity and residue data and build in a conservative safety factor. Alternatively, we 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, we 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?

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?

Issue 3: We are considering how we should inform the public of the import tolerance process while also ensuring that we do not disclose trade secrets and confidential commercial information.

Questions:

(a) Should we disclose to the public that we are considering an import tolerance for a new animal drug?

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

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

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

Issue 4: We are 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. We are seeking information on whether import tolerances will have a significant effect on the environment.

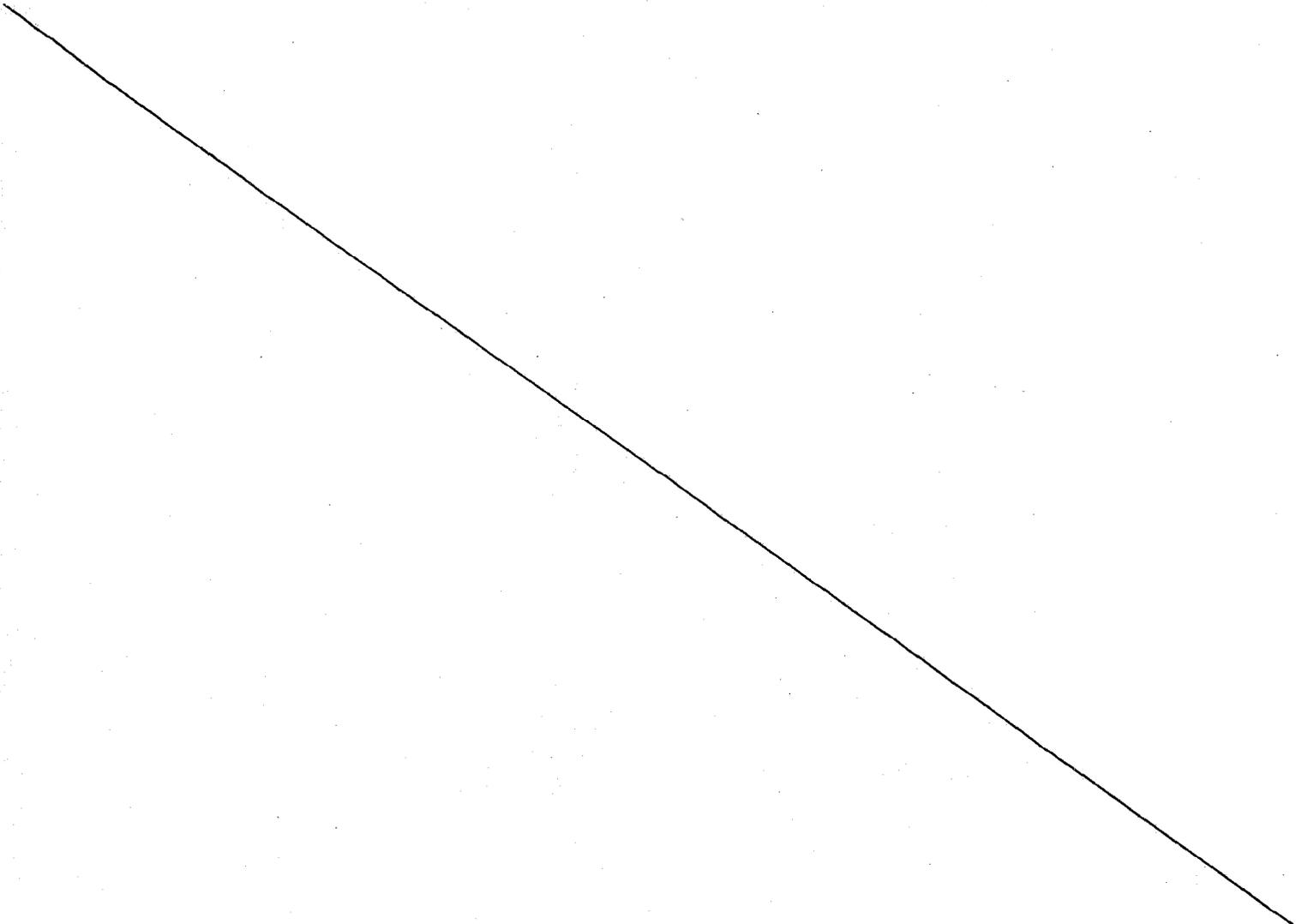
Issue 5: Please comment on any other aspects of import tolerances you wish to raise.

### III. Comments

Interested persons may submit written or electronic comments regarding the advance notice of proposed rulemaking by [*insert date 120 days after date of publication in the **Federal Register***]. Written or electronic comments should be submitted to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

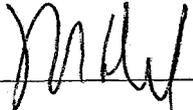
Comments may also be submitted electronically on the Internet at: <http://www.fda.gov/dockets/ecomments>. Once on this Internet site, select 01N-0284 Import Tolerances and follow the directions.

We intend to hold a meeting of the Veterinary Medicine Advisory Committee (VMAC) in September 2001. The committee will be asked to discuss answers to questions similar to those posed in the ANPRM. The notice of the date, time, and place for the meeting of the VMAC appears elsewhere in this issue of the **Federal Register**.



This ANPRM is issued under section 4(e) of the ADAA, sections 201, 402, 512, 701, and 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 342, 360b, 371, and 381), and under the authority of the Commissioner of Food and Drugs.

Dated: 7/16/01  
July 16, 2001.

  
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Margaret M. Dotzel,  
Associate Commissioner for Policy.

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