4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 514 and 556

[Docket No. FDA-2012-N-1067]

RIN 0910-AG17

New Animal Drugs; Updating Tolerances for Residues of New Animal Drugs in Food

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule; supplemental notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA or we) is proposing to amend our 2012 document entitled "New Animal Drugs; Updating Tolerances for Residues of New Animal Drugs in Food." The document proposed to revise the animal drug regulations regarding tolerances for residues of approved and conditionally approved new animal drugs in food by standardizing, simplifying, and clarifying the determination standards and codification style. We also proposed to add definitions for key terms. We are taking this action to more clearly explain our current thinking about certain provisions of the 2012 document based on comments from stakeholders, and to more accurately reflect the rationale FDA relied on in the past to approve certain new animal drugs without a tolerance. We are reopening the comment period only with respect to the specific issues identified in this supplemental proposed rule.

DATES: Submit either electronic or written comments on this proposed rule by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to http://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on http://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submission

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, FDA will post your comment, as well as any attachments, except for information

submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2012-N-1067 for this proposed rulemaking. Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at http://www.regulations.gov or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on http://www.regulations.gov. Submit both copies to the Division of Dockets Management. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: http://www.fda.gov/regulatoryinformation/dockets/default.htm.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to http://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dong Yan, Center for Veterinary Medicine (HFV-151), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-402-0825, dong.yan@fda.hhs.gov.

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Executive Summary

Purpose and Coverage of the Supplemental Notice of Proposed Rulemaking

We previously proposed to revise the animal drug regulations regarding tolerances for residues of approved and conditionally approved new animal drugs in food. In addition to proposing to standardize, simplify, and clarify the standards of determination and codification style for tolerances, we proposed a new definition section. In this document, we are proposing to revise or remove some of the previously proposed definitions, taking into account comments we received that have led us to clarify our current thinking, and to more accurately reflect the rationale FDA relied on in the past to approve certain new animal drugs without a tolerance.

Summary of the Major Provisions of the Supplemental Notice of Proposed Rulemaking

The previously proposed rule (2012 proposed rule) did not adequately explain our current view that methods other than the "regulatory method" derived from the method submitted by a sponsor as part of the new animal drug application can be used to determine the quantity of residue in edible tissues for surveillance and enforcement purposes. Therefore, we are removing the proposed definition for "regulatory method" and are reserving the term for use with carcinogenic compounds. We are also removing the use of this term from proposed § 556.5(d) (21 CFR 556.5(d)). We are proposing to revise portions of the 2012 proposed rule to better align the proposed rule with our current thinking and practice that an analytical method other than the

practicable method(s) submitted by the sponsor as part of the new animal drug application can be used for surveillance and enforcement purposes for non-carcinogenic compounds, as long as the performance criteria of that method are comparable to those of the practicable method. However, as described in section II.C, we are not proposing similar changes to the regulations concerning carcinogenic compounds because our current interpretation of the relevant provisions in the Federal Food, Drug, and Cosmetic Act (the FD&C Act) is that, unlike for non-carcinogenic compounds, the regulatory method prescribed in the approval of the new animal drug must be used for surveillance and enforcement purposes for carcinogenic compounds.

We are also revising the proposed definitions for "marker residue", "tolerance", "not required", and "zero". We are removing the definition for "acceptable single-dose intake" and adding a definition for "acute reference dose".

Table of Abbreviations and Acronyms

Abbreviation/Acronym	What It Means
ARfD	Acute reference dose
ASDI	Acceptable single-dose intake
CFR	Code of Federal Regulations
CVM	Center for Veterinary Medicine
FDA	U.S. Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
JECFA	World Health Organization/Food and Agriculture Organization of the United Nations Joint Expert Committee on Food Additives
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

I. Background

A. Introduction

In the Federal Register of December 5, 2012 (77 FR 72254), we issued a document to revise part 556 (21 CFR part 556) by standardizing and simplifying the codification style, revising the general considerations section, adding a scope section, and adding a definition section to define key terms used in the part. The definition section was proposed to include the terms used by FDA in the determination of tolerances. Some of the terms had been used

previously in part 556, but never defined, and some terminology that had been used was outdated or resulted in confusion to users of the part. We proposed a general considerations section (proposed § 556.5) to provide additional information and clarification for the tolerances listed in proposed subpart B. We are issuing this supplemental notice of proposed rulemaking to revise the proposed changes to part 556 to align with our current thinking.

B. Comments to the 2012 Proposed Rule for Updating Tolerances for Residues of New Animal Drugs in Food

We received several stakeholder comments to the proposed rule including a comment that requests clarification on the proposed definition for "regulatory method" and on the use of the term in proposed § 556.5(d), which stated that FDA requires that a drug sponsor develop a regulatory method to measure drug residues in edible tissues of approved target species. This comment notes that a regulatory method has historically been used to refer to the "required determinative and confirmatory procedures for regulatory surveillance of residue concentrations in meat products entering the food supply for comparison to the tolerance post-commercialization of the product." The comment also states the context of the proposal appears to be the method(s) used to collect data to support the setting of the tolerances preapproval. The comment also asks if the proposal implies that tolerances may be established using analytical procedures other than the determinative procedure. In addition, the comment states it should be clarified if regulatory method is referring to method(s) used preapproval for setting the tolerance versus a finite method(s) used for determining post-commercialization residue to compare to the tolerance.

We realize that the term "regulatory method" proposed in § 556.3 and used in proposed § 556.5(d) has caused some confusion. As a result of the comments, we are taking this

opportunity to better explain our current thinking about analytical methods used to determine residue levels in tissues for new animal drugs intended for use in food-producing animals.

II. Proposed Revisions to Subpart A--General Provisions

A. Analytical Method

An analytical method other than the practicable method can be used for surveillance and enforcement purposes for non-carcinogenic compounds, as long as the performance criteria (e.g., sensitivity, specificity, accuracy, and precision) of that method are comparable to those of the practicable method submitted by the sponsor as part of the new animal drug application. Such an analytical method would need to have the same capability as the practicable method to determine the quantity of the drug residues so that the tolerance, withdrawal period, or other use restrictions continue to ensure that the use of the drug will be safe. However, as described in section II.C, for carcinogenic compounds, the regulatory method prescribed in the approval of the new animal drug must be used for surveillance and enforcement purposes for carcinogenic compounds (see 21 CFR part 500, subpart E).

FDA establishes tolerances using the practicable method submitted by a sponsor as part of the new animal drug application as required by section 512(b)(1)(G) of the FD&C Act (21 U.S.C. 360b(b)(1)(G)). The practicable method has to meet certain performance criteria, including evaluation of accuracy, precision, and sensitivity. We use the practicable method submitted by the sponsor as part of the new animal drug application to determine the quantity of the drug residues that can safely remain in edible tissues (i.e., the tolerance), the withdrawal period, and any other use restrictions necessary to ensure that the proposed use of the drug will be safe, and make these use restrictions part of the conditions of approval. These conditions of use are designed to ensure that the proposed use of the drug will be safe § 514.1(b)(7) (21 CFR

514.1(b)(7)). In the past, the practicable method was often used for determining the quantity of residue in edible tissue when monitoring the food supply. However, as technologies have evolved, many of the older methods have become obsolete. In addition, there is an increased reliance on multiresidue methods in the monitoring of the food supply (i.e., methods that analyze for a number of different drug residues at the same time). As a result, we are clarifying that an analytical method other than the practicable method can be used for surveillance and enforcement purposes for non-carcinogenic compounds, provided it meets the same performance criteria as the practicable method to determine the quantity of the relevant drug residues. Therefore, we are proposing to revise some of the definitions in proposed § 556.3 of the 2012 proposed rule as well as revise some of the language under "General Considerations" in proposed § 556.5, to more accurately reflect our current thinking.

B. Proposed Revisions to Definitions (Proposed § 556.3)

In the 2012 proposed rule, we included a section of definitions (proposed § 556.3). We propose to revise four of the definitions, remove two definitions, and add a new definition in proposed § 556.3.

In the definition of "marker residue", we propose to delete "selected for assay by the regulatory method" because we are reserving the term "regulatory method" for use with carcinogenic compounds (see part 500, subpart E). Also, we propose to delete the explanatory text that follows the first sentence of the definition because an explanation of how the tolerance is used is not needed in this definition. In addition, we are removing the term "target tissue" in the definition and replacing it with "an edible tissue".

In the definition of "not required", we propose to more accurately reflect the rationale FDA relied on in the past to approve certain new animal drugs without a tolerance. Currently,

our general practice is to establish a tolerance for all new animal drugs we approve.

In the definition of "tolerance", we propose to delete the explanatory text that follows the first sentence of the definition because an explanation of how the tolerance is used is not needed in this definition.

In the definition of "zero", we propose to delete "when using a method of detection prescribed or approved by FDA" because, as discussed previously, an analytical method other than the practicable method can be used for surveillance and enforcement purposes for non-carcinogenic compounds. The additional proposed revisions to this definition are intended to clarify the meaning of the term "zero" as used in part 556 so that "zero" means any residues detected in the tissue renders it unsafe.

We propose to remove the definition of "acceptable single-dose intake (ASDI)". See discussion for "acute reference dose (ARfD)" further in this section for the explanation.

We propose to remove the definition of "regulatory method" because we are reserving the term "regulatory method" for use with carcinogenic compounds, consistent with our current interpretation of the FD&C Act (see part 500, subpart E).

We propose to add the definition of "acute reference dose (ARfD)" to mean "an estimate of the amount of residues expressed on a body weight basis that can be ingested in a period of 24 hours or less without adverse effects or harm to the health of the human consumer." ARfD would be used in place of ASDI wherever this term is currently used in the tolerances listed in subpart B of part 556.

In the 2012 proposed rule, we explained that sometimes the concept of an ASDI was used to calculate tolerances. We proposed to define the ASDI as "the amount of total residue that may safely be consumed in a single meal. The ASDI may be used to derive the tolerance for residue

of a drug at the injection site where the drug is administered according to the label." The definition of the ASDI was based on the U.S. Environmental Protection Agency definition of ARfD and chosen, in part, to provide additional clarity for the veterinary drug health based guidance value. Since that time, the use of the term ARfD has been more broadly applied by scientific and regulatory authorities, as further discussed in this section.

The United States is an active member of the Codex Alimentarius and the Codex Committee for Residues of Veterinary Drugs in Food, which rely on the World Health Organization/Food and Agriculture Organization of the United Nations Joint Expert Committee on Food Additives (JECFA) for scientific advice. The JECFA uses the guidance Environmental Health Criteria (EHC) 240, Principles and Methods for the Risk Assessment of Chemicals in Food in its evaluations (Ref. 1). This guidance defines and discusses the term ARfD. More importantly for FDA, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) has also developed guidelines that discuss the ARfD. The United States is a member of VICH and adopts finalized VICH guidelines for technical requirements for new animal drug approvals in the United States. On June 1, 2015 (80 FR 31041), we announced a draft guidance (Guidance for Industry #232 (VICH GL54)) entitled "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD)", in which the term "acute reference dose (ARfD)" is used to describe the same concept as the 2012 proposed definition of ASDI (Ref. 2). There are no fundamental differences between the meaning of ASDI and ARfD.

We consider it appropriate to propose using the VICH definition of ARfD to replace the 2012 proposed definition of ASDI. The ARfD may be used in the same manner as the ASDI,

which is to derive the tolerance for residues of a drug at an injection site where the drug is administered according to the label, or to derive the tolerance for residues of a drug in other edible tissues as a result of concern for the acute toxicity of the residues of the veterinary drug.

C. Proposed Revisions to General Considerations (Proposed § 556.5)

We propose to revise proposed § 556.5(d) to align with our current thinking. In addition, we propose to remove the term "regulatory method" from this provision because we are reserving this term for use with carcinogenic compounds (part 500, subpart E).

Although the proposed revisions would clarify that an analytical method other than the practicable method may be used for surveillance and enforcement purposes for residue levels of non-carcinogenic animal drugs, with regard to approved carcinogenic compounds, our current interpretation of the relevant provisions of the FD&C Act is that it requires that a regulatory method be prescribed for such a compound and used for surveillance and enforcement purposes. Under the Delaney Clause, section 512(d)(1)(I) of the FD&C Act, FDA cannot approve an application for a new animal drug if it is found to induce cancer when ingested by humans or animals. An exception to this provision, referred to as the DES (diethylstilbestrol) Proviso, allows for the approval of a carcinogenic compound if FDA finds that, under the approved conditions of use, the drug will not adversely affect treated animals and no residue of the drug will be found (by methods of examination prescribed or approved by the Secretary by regulations) (emphasis added) in any food for human consumption derived from the treated animals (see section 512(d)(1)(I)(i) and (ii) of the FD&C Act). FDA has issued regulations defining the operational definition of no residue and regulatory method for purposes of measuring carcinogenic compounds (21 CFR 500.82 and 500.88).

III. Proposed Conforming Change to 21 CFR Part 514

We are proposing a conforming change to the language in the introductory text of § 514.1(b)(7) by removing the term "regulatory" in the last sentence to reflect the fact that we are reserving this term for use with carcinogenic compounds. (See discussion in section II.C.)

IV. Legal Authority

Our authority for issuing this proposed rule is provided by sections 512(b)(1)(G) and (H), 512(d)(1)(F), 512(d)(2), 512(i), 571(a)(2)(A), and 571(b)(1) of the FD&C Act (21 U.S.C. 360b(b)(1)(G) and (H), 360b(d)(1)(F), 360(d)(2), 360b(i), 360ccc(a)(2)(A), and 360ccc(b)(1)). These provisions relate to the information new animal drug and conditional approval applicants provide with respect to proposed tolerances, withdrawal periods, and practicable methods, and the process by which FDA establishes and publishes regulations setting tolerances for residues of approved and conditionally approved new animal drugs. In addition, section 701(a) of the FD&C Act (21 U.S.C. 371(a)) gives FDA general rulemaking authority to issue regulations for the efficient enforcement of the FD&C Act.

V. Economic Analysis of Impacts

We have examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Orders 12866 and 13563 direct us to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). We believe that this proposed rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires us to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because this proposed rule would not impose compliance costs on the current or future sponsors of any approved and conditionally approved new animal drugs, we proposed to certify that the proposed rule would not have a significant economic impact on a substantial number of small entities.

The Unfunded Mandates Reform Act of 1995 (section 202(a)) requires us to prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $146 million, using the most current (2015) Implicit Price Deflator for the Gross Domestic Product. This proposed rule would not result in an expenditure in any year that meets or exceeds this amount.

VI. Paperwork Reduction Act of 1995

We tentatively conclude that this proposed rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Analysis of Environmental Impact

The Agency has determined under 21 CFR 25.30(i) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Federalism

We have analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. We have determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, we conclude that the proposed rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

IX. References

The following references are on display in the Division of Dockets Management (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at http://www.regulations.gov. FDA has verified the Web site addresses, as of the date this document publishes in the Federal Register, but Web sites are subject to change over time.

1. International Programme on Chemical Safety, "Environmental Health Criteria 240, Principals and Methods for the Risk Assessment of Chemicals in Food," 2009. (http://www.who.int/foodsafety/publications/chemical-food/en/). Accessed on February 11, 2016.

2. FDA, "Draft Guidance for Industry # 232: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish an Acute Reference Dose (ARfD), VICH GL54," (http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM448430.pdf), June 2015. Accessed on February 11, 2016.

List of Subjects

21 CFR Part 514

Administrative practice and procedure, Animal drugs, Confidential business information, Reporting and recordkeeping requirements.

21 CFR Part 556

Animal drugs, Foods.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR chapter I, subchapter E, be amended as follows:

PART 514--NEW ANIMAL DRUG APPLICATIONS

1. The authority citation for part 514 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 354, 356a, 360b, 360ccc, 371, 379e, 381.

§ 514.1 [Amended]

2. In § 514.1(b)(7) introductory text, remove the word "regulatory" from the last sentence.

PART 556--TOLERANCES FOR RESIDUES OF NEW ANIMAL DRUGS IN FOOD

3. The authority citation for part 556, as proposed to be revised on December 5, 2012 (77 FR 72254), continues to read as follows:

AUTHORITY: 21 U.S.C. 342, 360b, 360ccc, 371.

4. Amend § 556.3, as proposed to be added on December 5, 2012 (77 FR 72254), as follows:

a. Remove the definition of "Acceptable single-dose intake";

b. Add, in alphabetical order, a definition for "Acute reference dose";

c. Revise the definitions for "Marker residue" and "Not required";

d. Remove the definition of "Regulatory method"; and

e. Revise the definitions for "Tolerance" and "Zero".

The revisions and additions read as follows:

§ 556.3 Definitions.

* * * * *

Acute reference dose (ARfD) means an estimate of the amount of residues expressed on a body weight basis that can be ingested in a period of 24 hours or less without adverse effects or harm to the health of the human consumer.

* * * * *

Marker residue means the residue whose concentration is in a known relationship to the concentration of total residue in an edible tissue.

* * * * *

Not required, in reference to tolerances in this part, means that at the time of approval:

(1) No withdrawal period was necessary for residues of the drug to deplete to or below the concentrations considered to be safe, or an adequate withdrawal period was inherent in the proposed drug use, and there was a rapid depletion of residues, so there was no concern about residues resulting from misuse or overdosing; or

(2) No withdrawal period was necessary because the drug was poorly absorbed or metabolized rapidly so as to make selection of an analyte impractical or impossible.

* * * * *

Tolerance means the maximum concentration of a marker residue, or other residue indicated for monitoring, that can legally remain in a specific edible tissue of a treated animal.

* * * * *

Zero, in reference to tolerances in this part, means any residues detected in the tissue renders it unsafe.

5. Amend § 556.5, as proposed to be added on December 5, 2012 (77 FR 72254), by revising paragraph (d) to read as follows:

§ 556.5 General considerations.

* * * * *

(d) FDA requires that a drug sponsor submit a practicable method as part of their new animal drug application. FDA uses the practicable method to determine the quantity of the drug residues that can safely remain in edible tissues (i.e., the tolerance), the withdrawal period, and any other use restrictions necessary to ensure that the proposed use of the drug will be safe.

Dated: October 21, 2016.

Leslie Kux,

Associate Commissioner for Policy.

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