

FDLI PRIMER

FDA's Regulation of Veterinary Drug Products

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About This Primer

Under the Federal Food, Drug, and Cosmetic Act, before a new animal drug product may be sold in the United States, it must first obtain Food and Drug Administration (FDA) premarket approval to substantiate its safety and effectiveness for use under the conditions prescribed on the product label. This is intended to protect both the nation's animal and human populations from the detrimental impact of unsafe and dangerous unapproved drug products. Absent premarket review and approval, the general public is not in a position to determine whether a new product is safe, or the methods and controls used to manufacture, pack, store and ship the product are adequate. It is for this reason that FDA's regulation of new veterinary drug products is so important. This Primer was designed and drafted to provide the reader with an easy-to-use guide for navigating the U.S. FDA's new animal drug approval process. By including appendices at the end of the Primer on how veterinary drugs are governed in other countries, the editors also set out to provide readers with comparative information between some of the various international regulatory systems in the world.

About FDLI Primers

FDLI Primers are extensively researched, referenced and edited by some of the most experienced and respected professionals in the field. And, just like our flagship publication, the *Food and Drug Law Journal* (which has been published for more than six decades), you can rely on FDLI's reputation for fair, unbiased analysis and extensive and valuable sourcing and citation. Primers are practical, user-friendly and instantly available to you in PDF form online.

The Primers are designed to provide you with information and proprietary analysis to enable you to advise your clients or help your company comply with vexing issues, regulations and guidance. Each Primer is focused on a current issue that you or someone else at your firm or company is working on today—or tomorrow. And all Primers provide specific how-to guidance that will give you a thorough understanding of a complicated and often perplexing issue.

About FDLI

The Food and Drug Law Institute, founded in 1949, is a non-profit organization that provides a marketplace for discussing food and drug law issues through conferences, publications and member interaction. FDLI's scope includes food, drugs, animal drugs, biologics, cosmetics, diagnostics, dietary supplements, medical devices and tobacco. As a not-for-profit 501(c)(3) organization, FDLI does not engage in advocacy activities.

FDLI's Mission is to provide education, training and publications on food and drug law; act as a liaison to promote networking as a means to develop professional relationships and idea generation; and ensure an open, balanced marketplace of ideas to inform innovative public policy, law and regulation.

In addition to the Primer, FDLI publishes the quarterly, peer-reviewed *Food and Drug Law Journal* presenting in-depth scholarly analysis of food and drug law developments; *Update* magazine, which provides members with concise analytical articles on cutting-edge food and drug issues; and the Food and Drug Policy Forum, a biweekly publication providing a marketplace for the exchange of policy ideas regarding food and drug law issues.

Chapter VI

Human Food Safety

Madeleine M. McDonough and Lael A. Awong

The purpose of the human food safety regulations is to ensure that food is safe for human consumption regardless of the use of an animal drug in a food-producing animal.¹

A. Analysis of Drug Residues

To demonstrate “reasonable certainty of no harm” to humans as a result of the use of the new animal drug, drug sponsors carry the burden of showing that the new animal drug is safe for use and complies with Food and Drug Administration (FDA) regulations.² FDA regulations require that a New Animal Drug Application (NADA) describe the methodology for determining levels of drug residues to ensure that the proposed new animal drugs are safe for use in food-producing animals.³ Drug sponsors must conduct studies that demonstrate that “edible tissues from treated animals can be consumed daily in the human diet for a lifetime with no adverse effect”⁴ and report these findings to the Center for Veterinary Medicine (CVM) as part of the drug development, Investigative New Animal Drug (INAD) and NADA processes.

FDA implemented the requirements for analysis of residues in part 514.1 of title 21 of the *Code of Federal Regulations*, which specifies that the following information is required for inclusion in the NADA:

- “Complete experimental protocols for determining drug residue levels in the edible products, and the length of time required for residues to be eliminated from such products;”
- “residue studies conducted under appropriate (consistent with the proposed usage) conditions of dosage, time, and route of administration to show levels, if any, of the drug and/or its metabolites in test animals during and upon cessation of treatment and at intervals thereafter in order to establish a disappearance curve;”
- “if the drug is to be used in combination with other drugs, possible effects of interaction demonstrated by the appropriate disappearance curve or depletion patterns after drug withdrawal under appropriate (consistent with the proposed usage) conditions of dosage, time, and route of administration.”

To provide reliable data a sufficient number of the target species must be used, and drug residue levels should be determined in muscle, liver, kidney and fat, and where appropriate in skin, milk and eggs (yolk and egg white).⁵ The sponsor submission should also address the mechanism for administering the medication and maintaining records of consumption; testing for drugs intended for use in more than one species; and evaluation protocols where there are known or suspected drug residues in litter of treated animals.⁶

1 21 C.F.R. § 514.1(b)(8); 21 U.S.C. § 360(b).

2 21 C.F.R. § 514.1(b)(7).

3 *Id.*

4 See U.S. Dept. of Health & Human Servs, Food & Drug Admin., Center for Veterinary Medicine, Guidance for Industry, #61. FDA Approval of New Animal Drugs for Minor Uses and for Minor Species (May 29, 2008), available at <http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm>.

5 21 C.F.R. § 514.1(b)(7)(i).

6 *Id.*

FDA has also identified four primary areas that must be evaluated to ensure human food safety: 1) toxicology, 2) residue chemistry, 3) microbial food safety and 4) regulatory method relied upon by a sponsor.⁷

1. Toxicology

FDA and CVM define the “largest amount of the drug that will not harm people if they ingest that amount every day” as the acceptable daily intake (ADI). The type and extent of toxicological data required is determined based on the nature of the drug and the class of compounds to which the drug is related.⁸ Once ADI is determined, toxicological endpoints are examined to identify safe concentrations, which are considered in conjunction with tolerance levels (legal limit on the amount of drug residue in edible tissue) and withdrawal periods (drug-free period prior to slaughter) to determine permissible exposure levels.⁹

2. Residue Chemistry

As set forth above, sponsors must conduct residue chemistry studies, normally in the target species, in accordance with 21 C.F.R. § 514.1(b)(7)(i) and Good Laboratory Practices as described in 21 C.F.R. § 58. In the NADA, sponsors must provide the methodology for determining the residual quantities in or on food, the calculated target tissue and marker residue assignment, tolerance assignment and withdrawal times.¹⁰ The burden is placed squarely on the sponsor to demonstrate that residual effects of the new animal drug will not impact humans.

3. Microbial Food Safety

If a proposed drug has the ability to cause bacterial resistance, the drug sponsor must also provide a qualitative risk assessment to help CVM determine the potential impact of that resistance on public health.¹¹ FDA is focused on preventing “[h]uman illness, caused by an antimicrobial-resistant bacteria, attributable to an animal-derived food commodity, and treated with the human antimicrobial drug of interest.”¹²

A qualitative risk assessment procedure is recommended by FDA and has been used by a sponsor in at least one case to evaluate microbial food safety.¹³

This involved conducting 1) a release assessment to describe the probability that the antimicrobial new animal drug and its use in animals would result in the emergence and dissemination of resistant bacteria or resistance determinants in the food animal under the proposed conditions of use, 2) an exposure assessment to describe the likelihood of human exposure to the resistant bacteria or resistance determinants through consumption of edible products from treated animals and 3) a consequence assessment to describe the potential human health consequences of exposure to the defined resistant bacteria or resistance determinants by considering the human medical importance of florfenicol (the drug) in the treatment of human infectious disease.¹⁴

7 See *From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process*, available at http://www.fda.gov/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm219207.htm#Human_Food_Safety.

8 Guidance for Industry #61, *supra* note 4.

9 *Id.*

10 FOI Drug Summary for PENNCHLOR, available at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADDrugSummaries/ucm069887.pdf>.

11 U.S. Dept. of Health & Human Servs, Food & Drug Admin., Center for Veterinary Medicine, Guidance for Industry, # 152. Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern (Oct. 23, 2003), available at <http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052519.pdf>.

12 *Id.*

13 *Id.*

14 FOI Drug Summary for AQUAFLOL-CA1, available at <http://www.fda.gov/downloads/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADDrugSummaries/UCM050064.pdf>.

4. Regulatory Method Relied Upon by Sponsor

The final piece of the human food safety puzzle is ensuring that the methodologies employed by drug sponsors are appropriate. The NADA requires drug sponsors to identify the specific methodology of their studies (e.g., regulatory method for detection of residues), and the availability of the method (e.g., the validated regulatory method is available from CVM).¹⁵ CVM reviews the regulatory methods relied upon and confirms that appropriate testing methods were used for human food safety studies before approving new animal drugs.¹⁶

B. Regulating New Animal Drugs with Cancer-Causing Potential

Pursuant to section 512(d)(1)(I) of the Federal Food, Drug, and Cosmetic Act, known as the Delaney Clause, FDA is prohibited from using compounds found to induce cancer in humans or animals.¹⁷ However, new animal drugs that have the potential to create cancer-causing residues may be eligible for approval under an exception, often referred to as the Diethylstilbestrol (DES) Proviso, set forth in subpart E of part 500, title 21 of the *Code of Federal Regulations*.¹⁸ These regulations establish that such drugs may be approved if drug sponsors conduct Sensitivity-of-Method procedures and submit regulatory methods to establish that “no residue of that compound will be found in the food produced from those animals under conditions of use reasonably certain to be followed in practice.”¹⁹

At the outset, FDA conducts a threshold assessment of new animal drugs to determine if carcinogenicity testing is required.²⁰ FDA then evaluates the drug sponsor’s proposed regulatory methods and establishes the following measurements:

- “the concentration of a residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer” referred to as S_m ; and
- “the concentration of a residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to the human consumer” referred to as S_o .²¹

FDA assumes these amounts correspond with “the concentration of test compound in the total diet of test animals that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million.”²²

As explained in 21 C.F.R. § 500.86, drug sponsors must propose regulatory methods that will demonstrate the safety of the new animal drug by evaluating depletion rates of the residues of carcinogenic concern in edible tissues and target tissues identified by FDA.²³ FDA evaluates these rates and establishes marker residuals that allow it to make findings that the residue of carcinogenic concern does not exceed permissible levels in target

15 See FOI Drug Summary for PENNCHLOR, *supra* note 10.

16 See *From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process*, *supra* note 7.

17 21 C.F.R. § 500.80(a).

18 21 C.F.R. § 500, subpart E; Animal Drugs, Feeds, and Related Products; Regulation of Carcinogenic Compounds in Food-Producing Animals, 77 Fed. Reg. 50,591-50,593 (Aug. 22, 2012) (to be codified at 21 C.F.R. pt. 500); 21 C.F.R. § 514.1(b) (7)(ii); 21 C.F.R. § 500.84(3); see also Linda Bren, *Animal Health and Consumer Protection*, FDA CONSUMER MAGAZINE (The Centennial Edition January-February 2006), available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/AnimalHealthandConsumerProtection/default.htm>.

19 See Animal Drugs, Feeds, and Related Products; Regulation of Carcinogenic Compounds in Food-Producing Animals, 77 Fed. Reg. at 50,591-50,592; see also Bren, *supra* note 18.

20 21 C.F.R. § 500.80.

21 21 C.F.R. § 500.82.

22 *Id.*

23 21 C.F.R. § 500.86.

tissue, and, therefore, can be determined to be at a level that does not present a significant increase in risk of cancer to humans as a result of consumption in the human diet.²⁴

If drug sponsor studies are approved by FDA and successfully demonstrate that 1) there are no detectable levels of new animal drug residue in any food from the animal, and 2) the drug is effective and safe for the animal, the new animal drug may be eligible for approval.²⁵



Primer Pointers

- The Food and Drug Administration's (FDA's) human food safety regulations are meant to ensure that food intended for human consumption is safe regardless of the use of an animal drug in a food-producing animal.
- A New Animal Drug Application must include copies of the experimental protocols used to determine drug residue levels in edible tissue, total elimination rates, reports with analysis from the conducted drug residual studies and in cases where a drug is intended for use in combination with another drug product, assessment of the possible effects of such proposed interaction.
- For purposes of collecting a reliable data source, a sponsor is encouraged to use a sufficient number of the target species, and drug residue levels should be determined in muscle, liver, kidney and fat, and where appropriate in skin, milk and eggs (yolk and egg white).
- FDA has identified four primary areas requiring evaluation to ensure human food safety including toxicology, residue chemistry, microbial food safety and regulatory method relied upon by a sponsor.

²⁴ *Id.*

²⁵ *FDA Clarifies Regulation on Carcinogenic Compounds Used in Food-Producing Animals* (Aug. 22, 2012), available at <http://www.fda.gov/AnimalVeterinary/NewEvents/CVMUpdates/ucm316542.htm>.