U.S. FOOD & DRUG ADMINISTRATION

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RE: Docket Nos. FDA-2012-P-1252 and FDA-2020-P-1506

Dear Mr. Waltz, Ms. Wu, Ms. Connor, and Mr. Roach:

This responds to the citizen petitions dated December 20, 2012 ("2012 Petition")[1] and June 8, 2020 ("2020 Petition"),[2] submitted on behalf of the Center for Food Safety, Animal Legal Defense Fund, Food Animal Concerns Trust, and The Center for Biological Diversity. The 2012 petition requests that the Food and Drug Administration ("FDA") take the following actions with respect to the new animal drug ractopamine hydrochloride ("ractopamine"):

> (1) Immediately review the Codex Standards standards (sic) for ractopamine as established in July 2012;
>
> (2) Publish this Petition in the Federal Register as a proposal;
>
> (3) Provide opportunity for public comment on the Petition;

[1] Docket No. FDA-2012-P-1252
[2] Docket No. FDA-2020-P-1506

(4) Perform comprehensive scientific studies needed to characterize the health, welfare, and behavioral risks posed by the use of ractopamine in food-producing animals, including studies of animal toxicity of the drug with its metabolites (including, but not limited to, their genotoxicity, carcinogen[ic]ity, and any cardiovascular, reproductive, endocrine, musculoskeletal, or behavioral effects they may elicit); animal behavioral effects of the drug (including but not limited to social behaviors); and animal exposure to residues of the drug and its metabolites in edible tissues;

(5) Perform comprehensive scientific studies needed to characterize human food safety risks posed by the use of ractopamine in food-producing animals, including studies of human toxicity of the drug with its metabolites (including, but not limited to, their genotoxicity, carcinogen[ic]ity, and any cardiovascular, reproductive, endocrine, musculoskeletal, or behavioral effects they may elicit); and human exposure to residues of the drug and its metabolites in the edible tissues of food-producing animals;

(6) Perform comprehensive scientific studies to characterize the environmental risks posed by the use of ractopamine in food-producing animals; and

(7) Pending Codex review and comprehensive scientific study, significantly strengthen U.S. standards by:

a. Deviating from Codex standards for ractopamine and setting more health- and welfare-based standards;

or, in the alternative if FDA determines it will not or cannot perform this act:

b. Meeting Codex standards for ractopamine.

[2012 Petition pp. 1-2] We have carefully reviewed your petition and supporting material, subsequent information you submitted to the docket, comments submitted to the docket, and other information available to the Agency. For the reasons stated below, pursuant to 21 CFR § 10.30, we granted your request to provide an opportunity for public comment on the 2012 petition and we deny the remainder of your 2012 petition.

The 2020 Petition asserts that under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"), FDA has the authority to suspend and withdraw approval of new animal drugs if such drugs present an "imminent hazard" or are shown to be unsafe. The 2020 petition requests that the Commissioner "immediately suspend and/or withdraw the approval of ractopamine for use in pig and cow feed." We provided a partial response on December 17, 2020, in which we denied the

request to "use [our] authority to immediately suspend … the approval of ractopamine for use in pig and cow feed…" [2020 Petition p. 2]. Regarding the request to withdraw approval of ractopamine for use in swine and cattle, we have carefully reviewed your petition and supporting material and other information available to the Agency. For the reasons stated below, pursuant to 21 CFR § 10.30, we deny your 2020 petition.

I. BACKGROUND

Ractopamine hydrochloride ("ractopamine") was first approved in the United States in 1999 for use in swine for production purposes.[3] Since then, the drug has been approved for production purposes in cattle[4] and turkeys.[5] Ractopamine is also approved for use in swine, cattle, and turkeys in combination with other approved new animal drugs for production and therapeutic purposes. Currently there are 43 approved products, 9 of which are the subject of new animal drug applications (NADA), and 34 of which are the subject of abbreviated new animal drug applications (ANADA), also known as generic new animal drug applications.[6]

The FD&C Act requires that the safety of a new animal drug be determined "with reference to the health of man or animal," 21 U.S.C. § 321(u), and that in making a safety determination, the Secretary must consider factors relevant to health, specifically: probable consumption, cumulative effect, safety factors appropriate for animal experimentation data, and the likelihood that the conditions of use in the labeling will be followed, 21 U.S.C. § 360b(d)(2). For drugs used in food-producing species, FDA conducts both a human food safety evaluation and an animal safety evaluation. The animal safety evaluation differs depending on whether the drug is used for therapeutic purposes or production purposes. For drugs used for therapeutic purposes, FDA considers both health risks and health benefits to the target animal (i.e., the animal receiving the drug) and assesses whether the health benefit of the drug to the target animal outweighs its risks. *See United States v. Rutherford*, 442 U.S. 544, 555 (1979) ("[T]he Commissioner generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use."). For animal drugs used for production purposes (i.e., drugs that do not provide a therapeutic benefit to the target animal), CVM has applied a "manageable risk approach." *Stauber v. Shalala*, 895 F. Supp. 1178, 1191 (W.D. Wis. 1995). Under the manageable risk approach, CVM may approve a drug when it determines that a safety risk to animals can be mitigated through, for example, appropriate herd management techniques recommended on the drug labeling. *Id.* The FD&C Act does not prescribe the standard an applicant must meet to demonstrate safety, and consistent with congressional intent, FDA has never construed that standard to be "zero risk." *Id*. at 1184 ("The FDA has never applied a zero risk standard when assessing the safety of new animal drugs.").[7] CVM takes this approach

[3] NADA 140-863 (ractopamine hydrochloride approved for increased rate of weight gain, improved feed efficiency and increased carcass leanness in swine).
[4] NADA 141-221 (ractopamine hydrochloride approved for increased rate of weight gain, improved feed efficiency and increased carcass leanness in cattle).
[5] NADA 141-290 (ractopamine hydrochloride approved for increased rate of weight gain and improved feed efficiency in turkeys).
[6] https://animaldrugsatfda.fda.gov/adafda/views/#/search.
[7] FDA must interpret the statute to further congressional intent. *Teva Pharms., USA, Inc. v. FDA*, 182 F.3d 1003, 1011 (D.C. Cir. 1999). Many animal drugs are used for production purposes to increase the efficiency of livestock

because an interpretation of "safe" that requires zero risk for production use drugs would unnecessarily limit the use of such drugs, no matter how small or manageable the risks.

CVM applies the manageable-risk standard on a case-by-case basis. Each animal drug may pose different potential risks to different species, and there are many possible techniques for managing these risks. Therefore, CVM makes its approval decisions based on these specific circumstances and the likelihood of various risks. If new information comes to light regarding safety risks, CVM considers whether there are voluntary measures, such as labeling changes, that could address the safety risk and works with the drug sponsor to pursue these changes. CVM has historically pursued voluntary measures where possible, which can help prevent the need for withdrawing approval of a new animal drug; withdrawal often involves costly and lengthy proceedings. *See Natural Res. Def. Council, Inc. v. FDA*, 760 F.3d 151, 175 (2d Cir. 2014) (upholding FDA decision to pursue voluntary labeling changes to help avoid "a protracted administrative process and likely litigation"). In withdrawal proceedings under the general safety clause, CVM bears the initial burden of showing that new evidence raises questions about the drug's safety that are sufficiently serious to require the drug sponsor to demonstrate that the drug is safe. *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752 (D.C. Cir. 1980).

II. DISCUSSION

In considering the petitions, we reviewed all the information submitted with the petitions, as well as the additional articles subsequently submitted to the docket, and other information about the use of ractopamine in swine, cattle, and turkeys, including but not limited to adverse event reports submitted to FDA, FDA pharmacovigilance reviews, and reviews of additional scientific articles. The assertions made in the 2012 petition in support of the specific requests for FDA to perform studies on the use of ractopamine in swine, cattle, and turkeys and assertions made in the 2020 petition in support of withdrawing the approval of ractopamine for use in swine and cattle feed generally fall into the categories of animal safety, human food safety, and environmental impact. We note that your petitions make assertions with respect to the use of ractopamine in food-producing animals generally, although most references provided in the petitions pertain only to swine.

Our responses to each of your requests are discussed below.

production. *See, e.g., A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1486 (D.C. Cir. 1995) (describing "drug used to increase the rate of growth and feed efficiency in poultry"); *United States v. Pro-Ag, Inc.*, 968 F.2d 681, 682 (8th Cir. 1992) ("[P]roducts are intended to alter the structure or function of the body of animals by improving feed efficiency and increasing milk production and, thus, are drugs under the applicable law."). Congress did not intend these products to be held to an unrealistic zero-risk standard. For example, Congress instructed FDA to conduct additional research before banning subtherapeutic uses of antibiotics in animal feed (e.g., lower doses intended to improve weight gain and feed efficiency instead of treating disease) and specifically warned FDA against "regulation of products on theoretical grounds which are subject to scientific dispute." H.R. Rep. 97-172, at 105 (1982).

A. Immediately review the Codex Standards for ractopamine as established in July 2012.

The 2012 petition requests that FDA immediately review the Codex Standards for ractopamine as established in July 2012 by the Codex Alimentarius Commission.[8] [2012 Petition p. 1, 19] You cite to FDA regulations at 21 C.F.R. § 130.6 as support for your position that FDA must consider the Codex Standards. [2012 Petition p. 19, 26][9] You also argue that as a member of Codex, the U.S. is obliged to consider Codex Standards for adoption and that Congress intended for there to be an ongoing relationship between FDA and international food standard bodies, citing 21 U.S.C. § 360b(a)(6) and (b)(1) as allowing FDA to consider Codex Standards in establishing new animal drug tolerances. [2012 Petition p. 19] You argue that section 401 of the FD&C Act, 21 U.S.C. § 341, instructs the Secretary to promulgate regulations that will "promote honesty and fair dealing in the interest of consumers" and that, given the different standards (U.S. tolerances, Codex Standards, countries that have banned ractopamine), the requested action is necessary. [2012 Petition pp. 24-25]

We have considered your request to immediately review the Codex Standards for ractopamine as established in July 2012, along with the arguments in your petition and the supporting information you submitted. We interpret this request to be a review pursuant to section 401 of the FD&C Act and 21 CFR 130.6(a) because your petition relies on those citations. For the following reasons, we deny this request.

Under 21 CFR 130.6(a), "All food standards adopted by the Codex Alimentarius Commission will be reviewed by the Food and Drug Administration and will be accepted without change, accepted with change, or not accepted." The food standards to which 21 CFR § 130.6 refers are those that would be issued under section 401 of the FD&C Act (21 U.S.C. § 341), which gives FDA authority to promulgate regulations establishing standards of identity for food. The language of 21 CFR § 130.6(b) specifies how review of Codex Standards should be accomplished. For each provision, the regulation is clear that the standard would be proposed under section 401 of the FD&C Act.[10]

Section 401 of the FD&C Act provides that "[w]henever in the judgment of the Secretary such action will promote honesty and fair dealing in the interest of consumers, he shall promulgate regulations fixing and establishing for any food . . . a reasonable definition and standard of

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[8] The Codex Alimentarius Commission is a joint Food and Agriculture Organization (FAO) and World Health Organization (WHO) Food Standards Program established in 1963 that formulates voluntary international standards, codes of practice, and guidelines that constitute the Codex Alimentarius. Codex food standards recommend a definition or standard of identity for specific foods with the goal of ensuring fair practices in the food trade. The Codex also recommends maximum residue limits (MRLs) for veterinary drug residues in food products based on scientific evaluations provided by independent international risk assessment bodies or ad-hoc consultations. Codex food standards and MRLs are voluntary unless adopted by legislation.

[9] Footnote 118 of the 2012 petition cites 21 U.S.C. § 393(b)(1), (2)(A) as a basis for the assertion that all Codex Standards must be reviewed. However, 21 U.S.C. § 393 describes FDA's general mission and does not mention the Codex.

[10] To the extent your petition seeks adoption of maximum residue level (MRL) standards contained in the Codex Standards, we note that section 401 of the FD&C Act is inapplicable because MRLs are not definitions or standards of identity, quality, or fill of container. We further note that ractopamine hydrochloride Codex MRL standards exist only for cattle and pigs.

identity, a reasonable definition of quality, or reasonable standards of fill of container." 21 U.S.C. § 341. In this case, your request does not involve a food standard that establishes a definition or standard of identity, quality, or fill of container, but rather a review of the maximum residue levels (MRLs) set by Codex for the acceptable amount of drug residue in edible tissues of treated animals. Therefore, FDA does not agree that either section 401 of the FD&C Act or 21 CFR § 130.6 is applicable to your request for FDA to review the Codex Standards.

Your petition also cites 21 U.S.C. § 360b(b)(1) as the statutory basis of the requirement for FDA's consideration of Codex Standards; however, 21 U.S.C. § 360b(b)(1) does not mention Codex Standards. You also cite 21 U.S.C. § 360b(a)(6) which does refer to consideration of Codex Standards, but it allows such consideration in the context of establishing import tolerances for new animal drugs that are not subject to an approval. That provision is not applicable here, given ractopamine's approvals. You also refer to *Pineapple Growers Association of Hawaii v. FDA*, 673 F.2d 1083, 1084 (9th Cir. 1982), citing the notice of proposed rulemaking at 37 FR 21102 (October 5, 1972). That case is consistent with our conclusion that review of Codex Standards is required only for standards adopted under section 401 of the FD&C Act (21 U.S.C. § 341). As the Court explained:

> The United States is a member of the World Health Organization and of the Food and Agriculture Organization of the United Nations. The Codex Alimentarius Commission formed by those organizations adopts recommended standards for food products which member countries are then obliged to consider for adoption. *See* 37 Fed. Reg. 21102 (1972). In the United States this is done by FDA promulgation of regulations under § 341 [section 401 of the FD&C Act].

Pineapple Growers Ass'n, 673 F.2d at 1084. Because section 401 of the FD&C Act, 21 CFR 130.6(a), and the other provisions you have cited do not support your request to lower the currently approved tolerances for ractopamine, we deny this request.

B. Publish this Petition in the Federal Register as a proposal.

The 2012 petition requests that FDA publish this citizen petition in the Federal Register as a proposal that would require FDA to conduct several kinds of studies and to change the existing tolerance for ractopamine to the Codex Standards (or more stringent standards) pending completion of the studies. We deny this request.

In denying this request to publish the petition as a proposal in the Federal Register, we considered whether such publication would assist us in responding to the requests in your petition. FDA regulations at 21 CFR § 10.30(h) authorize the Commissioner to use several procedures in reviewing a petition, including the publication of a Federal Register notice requesting information and views[11] and a proposal to issue, amend, or revoke a regulation.[12] These procedures are discretionary, and in this case we determined that publishing your petition or a proposal to issue, amend, or revoke a regulation in the Federal Register would not assist us in addressing the issues you present in your petition. This is especially true because the public

[11] See 21 CFR § 10.30(h)(3).
[12] See 21 CFR § 10.30(h)(4).

can already submit comments and other input on a citizen petition through the Division of Dockets Management as part of FDA's citizen petition process. Therefore, FDA does not believe publishing your petition or a proposal to issue, amend, or revoke a regulation in the Federal Register would provide any additional assistance not otherwise available.

Because you specifically request FDA to review Codex Standards under 21 CFR § 130.6, we also considered whether that regulation provides a basis for publishing your request as a proposal. Subparagraph (b)(1) provides that the Commissioner shall publish a petition in the Federal Register as a proposal if the petition provides reasonable grounds for the proposed change. However, this subparagraph only applies to petitions requesting the adoption of a Codex Standard pursuant to section 401 of the FD&C Act (21 U.S.C. § 341). As explained above, section 401 of the FD&C Act does not apply to MRLs contained in the Codex Standards because MRLs are not definitions or standards of identity, quality, or fill of container. Therefore, the provisions in 21 CFR § 130.6 providing for publishing a petition in the Federal Register as a proposal likewise do not apply.

C. Provide opportunity for public comment on the Petition.

The 2012 petition requests that FDA provide an opportunity for public comment on the petition. We granted this request by posting your citizen petition to Regulations.gov, as required under FDA regulations, which allowed the public to comment on this request.[13]

FDA regulations provide that a citizen petition that appears to meet certain specified requirements will be filed by the Division of Dockets Management, with the date of filing, and assigned docket number. 21 CFR § 10.30(c). Your petition was filed by the Division of Dockets Management on December 20, 2012, and assigned the Docket Number FDA-2012-P-1252. FDA regulations further provide that an interested person may submit written comments to the Division of Dockets Management on a filed petition, and that those comments will become part of the docket file. 21 C.F.R. § 10.30(d).

FDA followed its normal procedures for accepting and filing your citizen petition, including making provisions for the public to comment on your petition. This response, which is being sent to the Division of Dockets Management, will be placed in the docket and it, along with the petition, all supporting documents, and the comments received on the petition, are part of the administrative record of this citizen petition. 21 C.F.R. § 10.30(i).

D. Perform comprehensive scientific studies needed to characterize the health, welfare, and behavioral risks posed by the use of ractopamine in food-producing animals, including studies of animal toxicity of the drug with its metabolites (including, but not limited to, their genotoxicity, carcinogeni[ci]ty, and any cardiovascular, reproductive, endocrine, musculoskeletal, or behavioral effects they may elicit); animal behavioral effects of the drug (including but not limited to social behaviors); and animal exposure to residues of the drug and its metabolites in edible tissues.

[13] https://www.regulations.gov/document/FDA-2012-P-1252-0001

The 2012 petition requests that FDA perform comprehensive scientific studies to characterize the health, welfare, and behavioral risks posed by using ractopamine in food-producing animals. As explained below, we deny your request.

Section 512(b)(1)(A) of the FD&C Act [21 U.S.C. § 360b(b)(1)(A)] requires sponsors of new animal drug applications, not FDA, to demonstrate safety.[14] This includes conducting studies to characterize the target animal safety of the drug. Although FDA has previously conducted some limited studies with respect to approved animal drugs, FDA does not have the facilities or personnel to conduct the types of studies required to support approval of animal drugs or to conduct the types of studies you are requesting in your petition. The responsibility to demonstrate safety remains on the sponsor throughout the lifecycle of the drug.[15]

Our review of the existing relevant safety information, including the scientific literature, post-market adverse event reports, and a study conducted by the drug sponsor, is discussed below.

E. Withdraw the approval of ractopamine for use in pig and cow feed under 21 C.F.R. § 558.500.

The 2020 petition requests that FDA withdraw the approval of ractopamine for use in pig and cow feed under 21 C.F.R. § 558.500. [2020 Petition p. 2] As explained below, we deny your request. We discuss your animal safety concerns in this section. To the extent you are requesting withdrawal based on human food safety concerns, we deny your request for the reasons explained in Section F.

As part of our post-approval responsibilities, we continuously monitor the safety of approved animal drugs throughout a drug's lifecycle through our pharmacovigilance program. This includes, but is not limited to, reviews of mandatory post-market adverse event reports submitted by the drug manufacturer, voluntary adverse event reports submitted by consumers, animal owners, producers, and veterinarians, drug experience reports submitted by the sponsor pursuant to FDA regulations, published and unpublished animal studies, and scientific literature. Our pharmacovigilance activities allow us to determine which, if any, post-approval regulatory activities are appropriate and how to prioritize such activities. These post-approval activities could include, but are not limited to, requiring additional or more frequent reporting from the applicant of the new animal drug,[16] requesting label changes for the safe use of the drug, requesting other changes to the labeled indications for use, requesting the sponsor perform additional studies, or initiating action to withdraw approval of the new animal drug.

[14] See Section 512(b)(1)(A), requiring an applicant to submit "full reports of investigations which have been made to show whether or not such drug is safe and effective for use[.]"
[15] For example, 21 CFR § 12.87(d) provides that in a formal evidentiary hearing on a denial of approval of a new animal drug application or a proposal to withdraw approval of a new animal drug application, the burden of proving the safety of the drug is on the person requesting approval or contesting withdrawal of approval.
[16] 21 U.S.C. 360b(l)(1); 21 CFR 514.80(b)(5)(i).

Consistent with our pharmacovigilance activities, we have reviewed the references you submitted in the 2012 and 2020 petitions.[17] However, many of the articles and reports of studies that you submitted as support for contentions related to "health, welfare, and behavioral risks" do not provide information specific to the target animal safety of the drug. For example, you submitted several reports of consumer preference surveys that indicate general consumer opinions and preferences about animal welfare and animal production practices.[18] These submissions do not provide any information relevant to FDA's evaluation of the safety of ractopamine to swine, cattle, or turkey. You also submitted trade press articles that do not provide any substantive information relevant to FDA's evaluation of the safety of ractopamine to swine, cattle, or turkey.[19] We also reviewed a book that you submitted containing a collection of articles by multiple authors that discuss various legal and ethical aspects of animal rights and

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[17] These references include, but are not limited to: R. Poletto et al., Aggressiveness and Brain Amine Concentration in Dominant and Subordinate Finishing Pigs Fed the β-Adrenoreceptor Agonist Ractopamine, 88 J. of Animal Sci. 3107, 3118 (2010), available at http://www.animalscience.org/content/88/9/3107.full.pdf; R. Poletto et al., Behavior and Peripheral Amine Concentrations in Relation to Ractopamine Feeding, Sex, and Social Rank of Finishing Pigs, 88 j. of Animal Sci. 1184, 1184 (2010), available at www.animalscience.org/contentf88/3/1184.full.pdf; B.W. James et Al., Effect of Dietary L-Carnitine and Ractopamine-HCL (Paylean) on the Metabolic Response to Handling Growth-Finishing Pigs, Swine Day 158, 158 &164 (2004); J.N. Marchant-Forde et al., The Effects of Ractopamine on the Behavior and Physiology of Finishing Pigs, 81 J. Animal Sci. 416, 416-17 (2003); Loneragan GH, Thomson DU, Scott HM (2014) Increased Mortality in Groups of Cattle Administered the b-Adrenergic Agonists Ractopamine Hydrochloride and Zilpaterol Hydrochloride. PLoS ONE 9(3): e91177. doi:10.1371/journal.pone.0091177; Liu et al., Ractopamine, a Livestock Feed Additive, Is a Full Agonist at Trace Amine-Associated Receptor 1, 350 J. Pharmacol. Exp. Ther. 124, 127 (July 2014); D. Courtheyn et al., Recent Developments in the Use and Abuse of Growth Promoters, 473 Analytic Chimica Acta 71 (2002); T.S. Edrington et al., Effects of Ractopamine HCL on Escherichia Coli O157:H7 and Salmonella in Vitro and on Intestional Populations and Fecal Shedding in Experimentally Infected Sheep and Pigs, 53 Curr. Microbiol. 82 (Jul. 2006).

[18] Robert W. Prickett, F. Bailey Norwood, & Jayson L. Lusk (2008), Consumer Preferences for Farm Animal Welfare: Results from a Telephone Survey of U.S. Households http://asp.okstate.edu/baileynorwood/Survey4/files/Robspaper.pdf , Master's Thesis, Oklahoma State University, Department of Agricultural Economics; Demeter Communications (2010), What 'Indicator Consumers' Want to Know Most About How U.S. Foods Are Produced http://demetercommunications.com/wp¬content/uploads/2010/04/REVFINAL.SegmenTrakExecSummary.4.28.10.pdf; Andrew Rauch & Jeff S. Sharp, Ohio State Univ., Ohioans' Attitudes About Animal Welfare (2005), available at http:/ohiosurvey.osu.edufpdf/2004_Animal_reportpdf; Glynn T. Tonsor & Christopher A. Wolf (2011) Kansas State University Mandatory Labeling of Animal Welfare Attributes: Public Support and Considerations for Policymakers http://www.agmanager.info/livestock/marketing/animalwelfare/AW-Labeling_FactSheet_07-19-11.pdf; Joseph Zogby, Zogby International, Nationwide Views on the Treatment of Farm Animals (2003), available at civileats.com/wp-content/uploads/2009/09/AWT-final-poll-report-10-22.pdf; U.S. Public's Awareness and Perceptions of Antibiotic Use in Food Animal Production, Applegate (2011); David S. Conner, Victoria Campbell-Arvai, & Michael W. Hamm, Consumer Preferences for Pasture-Raised Animal Products: Results from Michigan, 39 J. of Food Distribution Research 12 (2008).

[19] Helena Bottemiller, Dispute over Drug in Feed Limiting US Meat Exports, NBCNEWS.com (Jan. 25, 2012), http://business.nbcnews.com/_news/2012/01/25/10220221-dispute-over-drug-in-feed-limiting-us-meat-exports; Russia Throws Poisonous Meat Back to US, Pravda, Dec. 11, 2012, http://english.pravda.ru/business/companies/11-12-2012/123129-russia_usa_meat_imports-0/; Helena Bottemiller, U.S. and Russia Spar Over Ractopamine in Pork and Beef, Food Safety News, Dec. 18, 2012, available at http://www.foodsafetynews.com/2012/12/u-s-and-russia-spar-over-ractopamine-in-pork-and-beef/; Helena Bottemiller, U.S. Presses Taiwan on Ractopamine Ban, Food Safety News, Feb. 7, 2012, available at http://www.foodsafetynews.com/2012/02/us-presses-taiwan-on-ractopamine-ban/; Gretchen Goetz, Animal Drug Widely Used in US Meat the Focus of Trade Dispute, Food Safety News (Jan. 26, 2012), http://www.foodsafetynews.com/2012/01/a-controversial-animal-drug-banned; Helena Bottemiller, Behind the Global Fight Over Livestock Drug, Food & Environment Reporting Network, 2012, http://thefern.org/behind-the-global-fight-over-livestock-drug/ (last visited Dec. 13, 2012).

animal welfare.[20] This book makes no reference to ractopamine or beta-agonists and does not provide any substantive information relevant to FDA's evaluation of the safety of ractopamine to swine, cattle, or turkey.

1. Swine Review

CVM reviewed the safety of Paylean (Ractopamine hydrochloride) before approving the drug for use in swine in 1999. The target animal safety and drug tolerance study included 32 pigs (8 per group) dosed at 0 ppm, 20 ppm (1x dose), 100 ppm (5x dose), and 500 ppm (25x dose) Paylean in feed for 56 days. Pigs tolerated dietary levels up to 25 times the highest intended use level of ractopamine without physical signs of toxicity. A reproductive safety study was also conducted in gilts and, in that study, no toxicological effects were observed in pigs fed the highest intended commercial use level of 20ppm. The studies supporting substantial evidence of effectiveness included 583 crossbred finishing pigs (Dose Titration/Confirmation Clinical Effectiveness Trials For Performance Parameters) and 441 crossbred finishing pigs (Corroborative Dose Titration/Confirmation Clinical Effectiveness Trials For Performance Parameters). No adverse effects were observed for any treatments.

After receiving reports of an increase in downer pigs in slaughter plants, CVM requested that Elanco submit a supplemental NADA to revise the Paylean label to improve product safety and ensure that the most current information was available to producers. The label change was prompted by adverse event reports submitted to the center by Elanco, reports from USDA FSIS, and an Elanco-sponsored post-approval study. The original label was modified in 2001 by adding the following caution statement: "Caution: Pigs fed Paylean are at an increased risk for exhibiting the downer pig syndrome (also referred to as 'slows,' 'subs,' or 'suspects'). Pig handling methods to reduce the incidence of downer pigs should be thoroughly evaluated prior to initiating use of Paylean."

In a 2006 supplemental NADA approval, FDA halved the maximum dose from 20 ppm to 10 ppm and authorized the use of ractopamine in pigs weighing in excess of 240 lbs. Substantial evidence of effectiveness was determined through a pooled effectiveness study. Target animal safety was determined using data from three studies: a non-clinical laboratory study, the clinical field study, and a post-approval surveillance study. The supplement included an update to the caution statement on the labeling reflecting the results of these studies. The caution statement reads "CAUTION: Ractopamine may increase the number of injured and/or fatigued pigs during marketing. Not for use in breeding swine." The studies are summarized below.

- The non-clinical study results summary indicated that the feeding of ractopamine hydrochloride at 5 or 10 ppm up to 35 days was not associated with an increased incidence of abnormal health observations prior to the animals being exposed to a simulated marketing process. During a simulated marketing process, the feeding of ractopamine hydrochloride to heavyweight finishing swine was associated with an increase in the incidence of animals classified as ambulatory injured (i.e., obvious limp or injury), none of which required animals to be removed from the study.

[20] Cass Sunstein & Martha Nussbaum eds., Animal Rights: Current Debates and New Directions 4-5 (Oxford Univ. Press 2004), available at http://www.scribd.com/doc/63778967/Martha-Nussbaum-Animal-Rights-Current-De bates-and-New-Directions.

- The effectiveness field study concluded that during the marketing phase, ractopamine hydrochloride treatment was associated with an increased incidence of ambulatory injured animals.
- The Post Approval Surveillance study concluded that feeding ractopamine hydrochloride for 21 to 35 days at concentrations of 5 or 10 ppm to pigs weighing up to 240 lbs. can increase the number of non-ambulatory pigs often referred to as fatigued pigs.

We performed a comprehensive literature review for adverse events in swine fed ractopamine.[21] Overall, the literature suggests that pigs fed ractopamine may be more susceptible to metabolic and clinical signs of stress when subjected to stressful conditions, such as handling and transport. The results of one study found that pigs fed ractopamine (at 20 ppm, double the currently approved maximum dose of 10 ppm) have increased metabolic signs associated with stress (i.e., increased blood creatine kinase, blood lactate dehydrogenase, lactate, cortisol, and rectal temperature and decreased blood pH) under conditions of stress.[22] The literature further showed that pigs fed ractopamine demonstrated only mild differences in behavior compared to control pigs.[23] Finally, the literature also provided support that hoof lesions are more common in pigs fed ractopamine, which may lead to lameness; however, differences in clinical lameness associated with hoof lesions were not shown.[24]

We also analyzed adverse drug events in swine fed ractopamine reported to CVM. These adverse drug events included reports of death, recumbency, lethargy, lameness, and hyperactivity. Death is an outcome and was sometimes reported as a result of underlying factors. There were some reports of deaths with no listed underlying cause, which cannot be ruled in or out as possibly related to the feeding of ractopamine. Fatigued pig syndrome (including recumbency and lethargy) is a recognized risk associated with use of ractopamine in pigs and cautionary language is on the current labeling.

In response to the reports of lameness discussed above, Elanco Animal Health conducted a study to obtain information describing the current incidence of ambulatory injured pigs fed ractopamine, as compared to animals not fed ractopamine. We received a report of the study titled "Non-Clinical Laboratory Study: The Effects of Paylean® on Ambulatory Injury Incidence in Market Weight Swine During a Marketing Simulation Process" from Elanco Animal Health on December 20, 2023.[25] The study was designed to resemble commercial conditions during the marketing phase as closely as possible. Specifically, handling methods were intended to mirror

[21] The literature review was completed and contains literature found in the Embase database through December 1, 2024.

[22] James, B. W., M. D. Tokach, R. D. Goodband, J. L. Nelssen, S. S. Dritz, K. Q. Owen, J. C. Woodworth and R. C. Sulabo (2013). "Effects of dietary L-carnitine and ractopamine HCl on the metabolic response to handling in finishing pigs." Journal of Animal Science 91(9): 4426-4439

[23] Athayde, N. B., O. A. Dalla Costa, R. O. Roça, A. L. Guidoni, C. B. Ludtke, E. Oba, R. K. Takahira and G. J. M. M. Lima (2013). "Stress susceptibility in pigs supplemented with ractopamine." Journal of Animal Science 91(9): 4180-4187

[24] Poletto, R., M. H. Rostagno, B. T. Richert and J. N. Marchant-Forde (2009). "Effects of a "step-up" ractopamine feeding program, sex, and social rank on growth performance, hoof lesions, and Enterobacteriaceae shedding in finishing pigs." Journal of animal science 87(1): 304-313.

[25] Reference 1, Elanco Animal Health (December 20, 2023) "Non-Clinical Laboratory Study: The Effects of Paylean® on Ambulatory Injury Incidence in Market Weight Swine During a Marketing Simulation Process," CVM submission identifier N-140863-L-000998-G.

conditions on typical commercial US operations.[26] The study report concluded that the administration of ractopamine at 5, 7.5, or 10 ppm over a 30 to 31 day feeding period did not increase the frequency of market weight pigs classified as ambulatory injured, non-ambulatory injured, non-ambulatory non-injured, or dead during a simulated marketing process.

Based on our review of Elanco's study, CVM concludes that the handling methods used during the study may help manage safety risks to swine administered ractopamine. The study resembled commercial conditions, so we expect that these handling methods are commonly used already. The Pork Quality Assurance (PQA) and Transport Quality Assurance (TQA) standards have evolved over the years, with a focus on animal welfare.[27] Because the current labeling does not mention handling practices, FDA has concluded that label changes would affirm the need for the use of best practices in handling/management during transportation and marketing phases. Accordingly, CVM intends to seek voluntary modification of the approved labeling for ractopamine so that it includes appropriate handling instructions. Once these labels have been approved, CVM will continue to monitor adverse event reports and scientific literature as part of our ongoing pharmacovigilance review. This review will assist CVM in determining if further steps are necessary or if the labeling changes have sufficiently addressed any animal safety risks.

2. Cattle Review

CVM reviewed the safety of Optaflexx 45 (Ractopamine hydrochloride) before approving the drug in 2003 as a Type A Medicated Article for use in beef cattle.[28] The target animal safety study included 32 cattle (8 per group) dosed at 0 ppm, 30 ppm (1x dose), 90 ppm (3x dose), and 300 ppm (10x dose) Optaflexx in feed for 42 days. In addition, studies supporting substantial evidence of effectiveness included 860 heifers and 880 steers. No treatment-related adverse reactions or indication of safety concerns were observed in these larger feedlot trials conducted under commercial conditions. A supplemental approval for a new indication (use as a top dress feed) was approved in 2009 and the studies supporting substantial evidence of effectiveness included 560 steers. No treatment related adverse reactions or indication of safety concerns were observed in these additional effectiveness studies.

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[26] When moving animals throughout the entirety of the Marketing Simulation Phase, handlers followed Pork Quality Assurance (PQA) and Transport Quality Assurance (TQA) handling principles which included moving pigs at a normal walking pace, using animal handling tools appropriately to facilitate calm pig movement, no use of continuous noise when moving pigs, and no rough physical contact or willful acts of abuse when moving or interacting with pigs. No electric prods were used. This was consistent with PQA and TQA handling principles, which explain that prods increase stress in pigs and recommend using prods only as a last resort.

[27] Pork Checkoff (2021), PQA Plus Education Handbook Version 5.0, available at https://www.porkcdn.com/sites/lms/References+and+Resources/PQAv5+Handbook+English+2.8.22.pdf; *Pork* Checkoff (2023), Version 8 TQA Handbook, available at https://www.porkcdn.com/sites/lms/TQA/TQA_V8_Handbook_12.08.22_Final.pdf.

[28] FOI Summary Original New Animal Drug Application NADA 141-221 (2003) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/754; FOI Supplemental New Animal Drug Application (2009) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/755.

We reviewed the Loneragan publication[29] you provided, which identified an increased risk of death in feedlot cattle administered ractopamine and zilpaterol. Our review included an analysis of the study design, assessment, and conclusions. The Loneragan study concluded that the use of the beta-agonists ractopamine and zilpaterol in cattle is associated with an increase in cattle deaths.[30] Although the Loneragan study provides some evidence suggesting an increased mortality rate for cattle administered ractopamine, there are confounding aspects of the study and the results from this study should be interpreted with caution.

For ractopamine, the Loneragan retrospective study relied on a convenience sample of four companies willing to provide data (Companies A, B, C, and D). This means that there may have been selection bias (e.g., the decision to provide data may have been influenced by a suspicion of increased mortality) and the results from these four companies may not be generalizable to the target population. In addition, the article does not include data about cattle management practices, geographic location, and other company-specific information. Without this information, it is unknown whether any differences in cattle management practices, location, or other factors could explain the differences in death rates, separate from any potential impact of ractopamine administration, or whether different cattle management practices could manage or mitigate risk. The article did not provide the number of deaths per group at each company, though it did note that Company A did not see any deaths in cattle, whether administered ractopamine or not. The article found that the difference in mortality rates for cattle administered ractopamine at Companies B, C, and D was statistically significant, but the company datasets were not designed to investigate a direct association between ractopamine and mortality because the impact of other factors cannot be accounted for. Of the 79,171 cattle in the ractopamine dataset, there were 67 more deaths in cattle administered ractopamine compared to cattle that did not receive ractopamine (139 vs 72, respectively). This increase cannot be determined to be due to administration of ractopamine because of the limited information provided and other confounding factors of the study design. Given the limitations of this study, CVM concludes that the article does not show an unmanageable risk to cattle administered ractopamine.

We also performed a comprehensive pharmacovigilance review which included both a literature review[31] for adverse events (excluding the Loneragan study) and an analysis of adverse drug events reported to CVM. The analysis of adverse drug events reported to CVM included reports in which feedlot professionals reported an increase in mortality in cattle fed ractopamine; however, the reports are often difficult to assess. Death is an outcome and was sometimes reported as a result of underlying factors, most often due to respiratory disease (including Bovine Respiratory Disease (BRD) and Atypical Interstitial Pneumonia), or ruminal bloat. There were some reports of deaths, with limited details and no listed underlying cause, that cannot be ruled in or out as possibly related to the feeding of ractopamine. It is not possible to estimate real-world incidence using spontaneously reported data; however, the number of spontaneously reported adverse events mentioning death in cattle fed ractopamine averages from two to seven

[29] Loneragan GH, Thomson DU, Scott HM (2014) Increased Mortality in Groups of Cattle Administered the b-Adrenergic Agonists Ractopamine Hydrochloride and Zilpaterol Hydrochloride. PLoS ONE 9(3): e91177. doi:10.1371/journal.pone.0091177.

[30] Your citizen petitions did not request any actions with respect to zilpaterol. We note that zilpaterol is not currently marketed in the United States.

[31] The literature review was completed and contains literature found in the Embase database through December 1, 2024.

case reports a year. Additionally, the clinical sign "death" does not signal disproportionately for this product compared to other products in CVM's database. Given the limitations of our pharmacovigilance data, the review of reported adverse events mentioning death is inconclusive. Further information from cattle dying of unknown reasons, including necropsies to rule out other causes, would be needed to make a reliable assessment.

The pharmacovigilance review did identify other potential risks associated with the use of ractopamine including anxiety, hyperactivity, and aggression. Based on information available CVM concludes that better awareness, desensitization to procedures and implementation of low stress handling practices could manage these risks. The pharmacovigilance review also identified decreased appetite as a potential risk associated with the use of ractopamine. No information in the adverse event reports suggested that the decreased appetite was severe. In some reports the decrease in appetite appeared to be temporary and resolved while the animals remained on feed containing ractopamine and in other reports the decreased appetite resolved when use of ractopamine was discontinued.

Based on our review of the Loneragan study, adverse drug events, and other scientific literature, CVM concludes that changes in animal handling practices may help manage the risks to cattle safety. Although the Loneragan study provides some evidence of cattle safety risks, the risks do not appear to be consistent across the different cattle companies that provided data and there may have been selection bias from the companies that agreed to submit data. Nonetheless, CVM will seek label changes to encourage use of best practices for handling/transport focused on minimizing stress and will continue to monitor post-market adverse event reports for general trends and disproportionate signals.

3. Turkey Review

Although ractopamine for use in turkeys has not been marketed in the U.S. since 2015, we performed a comprehensive pharmacovigilance review including an evaluation of adverse events and a literature search.[32] We found some information in CVM's adverse drug event database to suggest a possible causal relationship between hyperactivity and hyperexcitability in turkeys administered ractopamine. We note, however, that the information is limited by the small number of cases and poor case quality.

Given that the drug has not been actively marketed for use in turkeys for almost a decade, along with the limited and less-than-robust information in CVM's adverse event database related to ractopamine use in turkeys, FDA does not believe it is a good use of agency resources to pursue any post-market activities, such as requesting labeling changes, for the ractopamine product approved for use in turkeys (Topmax). Should the product for turkeys become actively marketed again, CVM will reassess the need to pursue post-market activities.

[32] The literature review was completed and contains literature found in the Embase database through January 3, 2024.

4. Best Use of Limited Agency Resources

FDA has concluded that initiating proceedings to withdraw approval of ractopamine is not necessary at this time. Recent data indicates that recommended handling practices, which can be attained through voluntary labeling changes, can help manage existing safety risks. FDA has determined that it should seek these labeling changes. Agencies have broad discretion in prioritizing the best use of limited resources. *See Massachusetts v. EPA*, 549 U.S. 497, 527 (2007) ("[A]n agency has broad discretion to choose how best to marshal its limited resources and personnel to carry out its delegated responsibilities."); *Nat. Res. Def. Council, Inc. v. FDA*, 760 F.3d 151, 170–71 (2d Cir. 2014) ("Agencies have many responsibilities, and limited resources. Deciding whether and when to deploy those resources in an arduous, contested adversarial process is an important and difficult responsibility."). Even if CVM had concluded that grounds to initiate withdrawal proceedings existed, the process of withdrawing approval of animal drugs requires significant time and agency resources. Before FDA can withdraw approval, the drug sponsor has the right to notice and an opportunity to request a hearing. 21 U.S.C. § 360b(e). FDA's regulations provide the opportunity for a formal, evidentiary hearing if there is a genuine and substantial issue of fact. 21 CFR 12.21(a); 21 CFR 514.200(c)(1). After the administrative proceeding concludes, the drug sponsor may seek judicial review. 21 U.S.C. § 360b(h); 21 U.S.C. § 355(h). By pursuing voluntary measures, CVM can address animal safety concerns without the time and expense of an adversarial process.

F. Perform comprehensive scientific studies needed to characterize human food safety risks posed by the use of ractopamine in food-producing animals, including studies of human toxicity of the drug with its metabolites (including, but not limited to, their genotoxicity, carcinogeni[ci]ty, and any cardiovascular, reproductive, endocrine, musculoskeletal, or behavioral effects they may elicit); and human exposure to residues of the drug and its metabolites in the edible tissues of food-producing animals.

Your petition requests that FDA perform comprehensive studies to characterize human food safety risks posed by the use of ractopamine in food-producing animals. Section 512(b)(1)(A) of the FD&C Act requires sponsors of new animal drug applications, not FDA, to demonstrate safety. This includes conducting studies to characterize the human food safety of the drug. The responsibility to demonstrate safety remains on the sponsor throughout the lifecycle of the drug. We therefore deny your request for FDA to perform comprehensive scientific studies to characterize human food safety for the use of ractopamine in food-producing animals. To the extent you are requesting withdrawal based on human food safety concerns, we deny that request as well. As detailed below, FDA has determined that the current tolerances for ractopamine meet the legal safety standard (i.e., reasonable certainty of no harm).

Your request makes several claims with respect to the human health effects of the use of ractopamine in food-producing animals. You state that the drug is banned or its use restricted in 168 nations [2020 Petition p. 11],[33] and that some countries ban or restrict the import of products from animals treated with ractopamine. [2012 Petition pp. 7, 11-12] You also note that the

[33] In your 2012 petition, you state that ractopamine is banned or its use restricted in 160 nations [2012 Petition pp. 6-7].

existing Codex Standards MRLs are more stringent than FDA standards and assert that even those MRLs are not protective of human health [2012 Petition pp. 7, 28, 30] and that ractopamine has been linked to the poisoning of humans. [2012 Petition p. 6] You also express the view that existing studies are inadequate to justify the continued use of ractopamine [2012 Petition pp. 11, 13-14] and point to adverse drug event reports documenting 23 different types of medical symptoms in humans believed to be caused by the drug. [2012 Petition p. 15]

The information you present about other countries' bans and import restrictions is not directly relevant to whether the drug meets the human food safety requirements under the FD&C Act. FDA evaluated the safety of the drug in accordance with U.S. standards for safety, regardless of whether other countries ban or restrict imports of meat from treated animals. The FDA has reviewed the same studies performed by the drug sponsor that formed the basis for decisions by the European Union, Russia, and China regarding ractopamine. Based on our review of these studies and the underlying reasons for the bans and restrictions, FDA concludes that the current tolerances for ractopamine ensure a reasonable certainty of no harm to human consumers.

The European Union and several other nations have legislation which does not permit the use of beta-agonists for growth promotion in food-producing animals (EC Directive 96/22/EC),[34] while the U.S. does not have non-therapeutic restrictions. The Russian Federation does not allow for the use of ractopamine because it disagrees with the Codex Alimentarius Commission's level of substantiation for the acceptable daily intake of ractopamine.[35] The Russian Federation's ractopamine assessment is based on an evolutionary model for risk to the cardiovascular system which is not a well-established methodology; additionally there is no data to support the assertion that chronic consumption of ractopamine residues leads to increases in heart rate and subsequent changes in cardiovascular function in the human population. Therefore, the Russian Federation's assessment does not change FDA's opinion. China banned ractopamine primarily based on concerns regarding the concentrations of ractopamine residues found in pig offal organs, notably lung,[36] which are more frequently consumed in China than in the United States. The FDA has evaluated the tissues generally consumed by U.S. consumers (muscle, liver, kidney, and fat)[37] in the human food safety assessment for ractopamine. FDA does not evaluate the safety of lung tissue because the sale of animal lungs for human consumption is banned in the United States. 9 CFR 310.16(a).

Your petition also asserts that "[r]actopamine residue in animal tissue has been linked to poisoning of humans." [2012 Petition p. 6] We were unable to find any information to substantiate that ractopamine, when used as approved in the U.S., has been linked to poisoning of humans. One of the references you provided to support your assertion states that "[b]ecause residues in animal tissues have been linked to some poisoning cases in humans (Kuiper, et al., 1998), most of the β-adrenergic agonists except ractopamine, which was recently licensed as a

[34] Council Directive 96/22/EC of 29 April 1996 concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of ß-agonists, available at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31996L0022.

[35] N.V. Zaitseva et al., (2014) Health Risk Assessment of Exposure to Ractopamine Through Consumption of Meat Products, International Journal of Advanced Research. Vol. 2: 538-545

[36] JECFA FAO Monograph 9 (2010) http://www.fao.org/fileadmin/user_upload/vetdrug/docs/9-2010-ractopamine.pdf

[37] Edible tissues are defined in U.S. Code of Federal Regulations Title 21, part 556.3 (21 CFR 556.3)

swine feed additive in the United States, are now prohibited from use as feed additives in food animals."[38] The article goes on to speculate that there could be adulteration of feed with ractopamine residues and states that there is a need for a "rapid, sensitive, and economical method for detecting ractopamine in animal feeds." Neither the article itself, nor the Kuiper et al. article[39] it references, supports the assertion that ractopamine residues have been linked to poisoning in humans.

The other reference you cite in support of the assertion that ractopamine residues have been linked to the poisoning of humans is an article published on the website www.AlterNet.org.[40] That article asserts that more than 1,700 people were "poisoned" from eating Paylean-fed pigs since 1998. The article attributes that figure to the Sichuan Pork Trade Chamber of Commerce. The opinion article provides no information about or citation for this statement. Various publications in the scientific literature have reported the same statistic due to illegal use of clenbuterol in swine many years ago.[41] Clenbuterol, also a member of the beta-agonist family, is approved only for use in horses in the United States. 21 CFR 520.452. However, it is prohibited for use in food-producing animals. 21 CFR 530.41(a)(2). Clenbuterol presents different safety concerns than ractopamine because ractopamine has a much shorter half-life, is more readily inactivated in the liver, is eliminated faster, and has a lower potential for bioaccumulation. Therefore, it is not appropriate to consider that all compounds of the beta-agonist family have the same safety profile. Based on our review of the literature, FDA is not aware of any reports of human food safety concerns for ractopamine when used in food-producing animals according to the approved labeling. Without additional information regarding the assertion, for example, about whether the claimed "poisonings" were the result of misuse of ractopamine, etc., FDA cannot draw any conclusions regarding food safety, nor base any decisions on this claim.

You also express your views that existing studies are inadequate to justify the continued use of ractopamine. [2012 Petition pp. 11, 13-14] FDA notes that applicants of new drug applications are required to submit full reports of investigations which have been made to show whether such drug is safe and effective for use. 21 U.S.C. § 360b(b)(1)(A). In determining whether ractopamine is safe for its intended uses, FDA considered the probable consumption of ractopamine in food, the cumulative effects of ractopamine on humans, appropriate safety factors to reflect uncertainties associated with extrapolation of animal data to humans, and the appropriateness of the proposed tolerances. 21 U.S.C. § 360b(d)(2). For the approval of ractopamine, FDA considered both acute and chronic exposure of people to residues of

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[38] J.P. Wang, S.X. Shen, Technical Note: A Monoclonal Antibody-Based Immunoassay for Determination of Ractopamine in Swine Feeds, 84 J. of Animal Sci. 1248, 1248 (2006).
[39] H.A. Kuiper, M. Y. Noordam, M.M.H. van Dooren-Flipsen, R. Schilt, A.H. Roos. (1998). Illegal use of β-adrenergic Agonists: European Community. J. Anim. Sci. 76:195–207.
[40] Martha Rosenberg, 'Why Has the FDA Allowed a Drug Marked "Not Safe for Use in Humans" to be Fed to Livestock Right Before Slaughter?' AlterNet.org (February 2, 2010), https://web.archive.org/web/20100206211944/http://www.alternet.org/story/145503/why_has_the_fda_allowed_a_drug_marked_'not_safe_for_use_in_humans'_to_be_fed_to_livestock_right_before_slaughter.
[41] Zhou G, Zhang W, Xu X. China's meat industry revolution: challenges and opportunities for the future. Meat Sci. 2012 Nov;92(3):188-96. doi: 10.1016/j.meatsci.2012.04.016.; 1.
Wang Y, Lau K, Lau F. Clenbuterol Food Poisoning from Snake Meat Consumption: An Outbreak of 13 Cases. Hong Kong Journal of Emergency Medicine. 2015;22(1):46-49. doi:10.1177/102490791502200106

ractopamine in food.[42] There is a significant body of data pertaining to human safety and ractopamine residues in food. This includes information regarding the receptor pharmacology of ractopamine hydrochloride, and the impact of ractopamine on adrenergic receptor activity and binding affinity, acute toxicity, subchronic and chronic general systemic oral toxicity, reproductive toxicity, developmental toxicity, genetic toxicity, carcinogenicity, and antimicrobial activity across rodents, dogs, primates, swine, and humans.[43]

FDA established an acceptable daily intake (ADI) of 1.25 microgram per kg body weight per day in the human diet. 21 CFR 556.570. The ADI is the daily human dietary intake which, during up to an entire life of a human, appears to be without adverse effects or harm to the health of a consumer. The ADI is based on the toxicology studies and other applicable scientific information and reflects the uncertainties with the information. The studies submitted in the new drug applications for ractopamine were extensively reviewed by FDA prior to approval, and the safety of ractopamine continues to be monitored and evaluated through adverse drug event reports and other sources of information. The JECFA[44] has reviewed the available data on ractopamine and performed comprehensive safety assessments considering its toxicology, residues in and intake from food animals in 1993, 2004, 2006, and 2010. There was agreement in the toxicological evaluation of ractopamine by FDA and JECFA. Indeed, the difference between the JECFA ADI of 0 to 1 microgram per kg body weight per day and the FDA ADI of 1.25 microgram per kg body weight per day is solely a reflection of the JECFA practice of rounding to one significant digit. The ADI value derived for swine also applies to the cattle and turkey approvals.

In addition, as part of the new animal drug application review process, FDA evaluated the submitted studies to determine appropriate tolerances for ractopamine residues in the muscle and liver tissues of cattle, swine, and turkeys, to ensure that meat from these animals is safe for human consumption. These studies included total radiolabeled residue studies, comparative metabolism studies, cold residue depletion studies, method validation, and method transfer studies. FDA considered data and responses from all the studies performed with ractopamine in its human food safety evaluation of this drug. These studies appropriately characterized the residues of ractopamine and their metabolites and were sufficient to determine the appropriate tolerances that present a reasonable certainty of no harm to human health from the use of ractopamine in food-producing animals. A summary of these studies for each of the approved uses of ractopamine is available on FDA's website.[45] Tolerances for ractopamine hydrochloride

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[42] See, Guidance for Industry #3. General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals. https://www.fda.gov/media/70028/download.

[43] See, NADA 140-863 FOI summary, page 29 et seq., https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/507

[44] The JECFA is an international scientific expert committee administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO). It has been meeting since 1956, to evaluate the safety of food additives, contaminants, naturally occurring toxicants and residues of veterinary drugs in food. JECFA serves as an independent scientific expert committee, which performs risk assessments and provides advice to FAO, WHO, and the member countries of both organizations, as well as to the Codex Alimentarius Commission (CAC). Based on their scientific evaluation, the JECFA recommends MRLs for adoption by the CAC (Codex MRLs).

[45] NADA 140-863 (1999) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/507; NADA 141-221 (2003) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/754; NADA 141-221 (2009) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/755; NADA 141-290 (2008) https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/854;

are codified in 21 CFR 556.570. Tolerances for cattle liver are 0.09 ppm (90 ppb, or 90 µg/kg of liver) and 0.03 ppm in cattle muscle (30 ppb, or 30 µg/kg of muscle). For swine, the tolerances are 0.15 ppm in liver and 0.05 ppm in muscle. For turkeys, the tolerances are 0.45 ppm in liver and 0.1 ppm in muscle. Both FDA and JECFA followed the normal procedures of their respective organizations to establish tolerances and recommend MRLs. The procedure for establishing an FDA tolerance differs from that for establishing a Codex MRL.[46] FDA sets the tolerance at the level necessary to ensure safety; residue levels above the tolerance are considered unsafe. By contrast, the procedure to establish a MRL often factors other components into the evaluation, such as the percentage of the ADI needed to adhere to the residue concentrations in the tissues based on the conditions of use. In other words, the MRL may be lower than the highest safety level if the conditions of use are likely to result in much lower residues. Therefore, a residue value above the MRL may still be considered safe.

Finally, you assert that adverse drug event reports document 23 different types of medical symptoms in humans believed to be caused by the drug. [2012 Petition p. 15] As noted on FDA's website,[47] adverse drug event reports are an important source of information to FDA and provide an early warning that there may be adverse effects not detected during pre-market testing of FDA-approved animal drugs. FDA monitors these reports to make decisions about product safety which may include changes to the label or other regulatory action.

Of the adverse drug event reports you reference that were submitted to FDA, only three were potentially related to oral human exposure to ractopamine. One of the adverse drug event reports involves a potential exposure to ractopamine residue in swine tissues. This adverse drug event was submitted by a swine owner who fed and slaughtered pigs for his family. He reported that a family member developed a muscular condition after consuming the pork and he was concerned that a feed mill may have made a mistake and mixed a high level of ractopamine in the swine feed. There was no other information provided or any confirmation of exposure. Another adverse drug event report involved a patient who, sometime after consuming bacon for breakfast and lunch, was hospitalized after experiencing a weakened heart, irregular heartbeat, and multiple loss of consciousness. The patient reported general knowledge that ractopamine is fed to pigs and the dangers of the product to humans and animals. The adverse drug event report noted that the patient had a history of heart failure. Further attempts to follow-up with the patient were not successful. The third adverse drug event report contained the internet news article discussed above that attributed the statement that there were over 1,700 poisonings from Paylean-fed pigs to the Sichuan Pork Trade Chamber of Commerce.[48] Again, no information was submitted to substantiate this statement. Since 2010, no adverse effects in humans related to consumption of

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[46] General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals, Guidance for Industry #3 at 19-20 (May 2022), https://www.fda.gov/media/70028/download. ("Tolerances and MRLs are both numbers that describe the limits of residues. However, tolerances and MRLs are not derived in the same manner and are used for different purposes. At times, it may be appropriate to harmonize the tolerance with an already established MRL.")

[47] https://www.fda.gov/animal-veterinary/product-safety-information/adverse-event-reports-animal-drugs-and-devices

[48] Martha Rosenberg, 'Why Has the FDA Allowed a Drug Marked "Not Safe for Use in Humans" to be Fed to Livestock Right Before Slaughter?' AlterNet.org (February 2, 2010) https://web.archive.org/web/20100206211944/http://www.alternet.org/story/145503/why_has_the_fda_allowed_a_drug_marked_'not_safe_for_use_in_humans'_to_be_fed_to_livestock_right_before_slaughter.

edible tissues from ractopamine treated animals have been reported to FDA or described in the literature.

G. Perform comprehensive scientific studies to characterize the environmental risks posed by the use of ractopamine in food-producing animals.

Your petition requests that FDA perform comprehensive scientific studies to characterize the environmental risks posed by the use of ractopamine in food-producing animals. You assert that "studies suggest that ractopamine may also be detrimental . . . to the environment." [2012 Petition p. 3] You argue that FDA has not completed an extensive review of the potential environmental effects of ractopamine and claim that the Agency's environmental analysis found a "high amount of uncertainty" associated with chronic exposure to ractopamine. [2012 Petition pp. 3, 30] For the following reasons, we deny your request.

Under the National Environmental Policy Act (NEPA) (42 U.S.C. § 4321, *et seq.*), federal agencies must prepare a statement on the potential environmental impacts of all major Federal actions significantly affecting the quality of the human environment (42 U.S.C. § 4332(2)(c)(i)). Agencies are not required to prepare an environmental impact statement if the proposed action qualifies for a categorical exclusion (42 U.S.C. § 4336(a)(2)) or if an environmental assessment is performed that results in a finding that the action will not have a significant impact on the human environment (42 U.S.C. § 4336(b)(2)).[49] FDA's regulations specify that all applications or petitions requesting Agency action include an environmental assessment or claim of categorical exclusion. 21 C.F.R. § 25.15(a). Although applicants for new animal drug approvals are often responsible for preparing the environmental assessment, FDA is ultimately responsible for its final scope and content and adopts the environmental assessment as its own following approval, unless the action is in a specific class that qualifies for a categorical exclusion. See 21 C.F.R. § 25.20(m). FDA evaluates the information contained in the environmental assessment to determine whether it is accurate and objective, whether the proposed action may significantly affect the quality of the human environment, and whether an environmental impact statement will be prepared. 21 CFR § 25.15(b).

We are denying your request that comprehensive scientific studies be conducted to characterize the environmental risks posed by the use of ractopamine in food-producing animals because we do not believe that additional studies are warranted. The applicant conducted comprehensive scientific studies and submitted environmental assessments as part of each single ingredient

[49] FDA followed the then-existing NEPA regulations issued by the Council on Environmental Quality (CEQ) at 40 CFR Parts 1500 to 1508 when it published the environmental assessment and finding of no significant impact for ractopamine. Those regulations were subsequently amended, and CEQ recently published an interim final rule to rescind its regulations based on a lack of legal authority. 90 FR 10610, 10613 (Feb. 25, 2025); *see Marin Audubon Society v. FAA*, No. 23-1067 (D.C. Cir. Nov. 12, 2024) (stating that CEQ lacks authority to issue binding NEPA regulations); *Iowa v. CEQ*, No. 1:24-cv-00089 (D. N.D. Feb. 3, 2025) (vacating 2024 CEQ regulations after concluding CEQ lacked rulemaking authority). Because FDA has promulgated its own NEPA-implementing regulations in consultation with CEQ, *see* 42 U.S.C. § 4332(2)(B) (requiring Federal agencies to develop methods and procedures to implement NEPA in consultation with CEQ), we cite to the statute and our own regulations.

NADA for ractopamine.[50] Prior to approving the NADAs, FDA evaluated the environmental assessments and found that they contained sufficient information to determine that approving the applications would not significantly impact the quality of the human environment.[51] See 21 C.F.R. § 25.15(a)-(b). You provide no evidentiary basis for contesting these findings but merely make conclusory statements about their adequacy.[52]

Additionally, we note that toxicity assays have been conducted on a variety of sensitive surrogate non-target organisms, including bobwhite quail, mallards, rainbow trout, bluegill, *Daphnia magna*, algae, earthworm, and seedlings. These assays did not reveal any adverse environmental effects to these species at the expected level of exposure when the products are used according to their labeled instructions. The environmental evaluation of ractopamine has been comprehensive and has adequately addressed potential impacts from acute and chronic exposures from individual, single farm scenarios and multiple concurrent uses on a watershed scale (i.e., cumulative scenarios).

Finally, you asserted that the Agency's own NEPA analysis concluded that there existed a "high amount of uncertainty" associated with chronic exposure to ractopamine, and that such a drug cannot reasonably be safe and effective. [2012 Petition pp. 3, 30] In the Finding of No Significant Impact issued in December 2000 for OPTAFLEXX 45 Type A Medicated Article, FDA stated,

> With regard to chronic exposure risks to aquatic organisms, there were no quantitative data submitted to address this issue. Estimates made using acute exposure and toxicity data indicate that chronic toxicity is not expected but suggest a possible chronic exposure risk from incremental increases in ractopamine hydrochloride from multiple site uses in cattle and swine feed. There is a high amount of uncertainty associated with this observation. To reduce the uncertainty, it is important to generate additional data to assist in characterizing chronic risk to aquatic species. Elanco has agreed to generate data for chronic toxicity to aquatic invertebrates and a quantitative estimate of chronic exposure on a local and a watershed basis. Since these data are primar[il]y to reduce uncertainty, these data are not required at this time but must be provided in the next application to

[50] NADA 140-863 – Environmental Assessment for swine dated 1995, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/165; NADA 141-221 – Environmental Assessment for cattle dated 1998, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/166; NADA 141-290 – Environmental Assessment for turkeys dated 2001, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/803.

[51] NADA 140-863, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/165; NADA 141-221, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/166; NADA 141-290, FONSI dated 2003, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/803.

[52] Not only were the environmental assessments adequate, but despite being conducted before FDA published its Guidance for Industry #166 (Environmental Impact Assessment for Veterinary Medicinal Products – Phase II), most of the studies recommended by that guidance were conducted and submitted as part of the evaluation of the environmental fate, exposure, and effects of ractopamine.

determine whether additional data are needed or risk management is necessary for ractopamine use.[53]

The uncertainty expressed was related to the observation that there may be a possible chronic exposure risk from incremental increases in ractopamine hydrochloride from multiple site uses in cattle and swine feed. In any event, the applicant generated data for chronic toxicity to aquatic invertebrates and a quantitative estimate of chronic exposure on a local and a watershed basis in the subsequent 2001 TOPMAX environmental assessment for turkeys[54] and FDA determined there were no concerns.[55]

Because you have not provided any evidence or information to support the need for additional comprehensive scientific studies to characterize the environmental risks posed by the use of ractopamine in food-producing animals, FDA denies your request.

H. Pending Codex review and comprehensive scientific study, significantly strengthen U.S. standards by: a. Deviating from Codex standards for ractopamine and setting more health- and welfare-based standards; or, in the alternative if FDA determines it will not or cannot perform this act: b. Meeting Codex standards for ractopamine.

Your 2012 petition requests that, pending the reviews and studies you ask FDA to perform, FDA set more stringent health and welfare-based standards than those set by Codex or, alternatively, that FDA adopt the Codex standards for ractopamine MRLs. We deny your request for the following reasons.

Under section 512(b)(1)(H) of the FD&C Act, sponsors are required to submit the proposed tolerance as part of the application for approval. The proposal should include "a practicable method to determine the quantity of the drug residues that can safely remain in edible tissues (i.e., the tolerance)…to ensure that the proposed use of the drug will be safe." 21 CFR 556.5(d). We reviewed human food safety, including the tolerance proposal, during our review of the ractopamine NADAs. For ANADA approvals, under section 512(n)(1)(A)(ii) of the FD&C Act, the sponsor must provide information to show that the residues of the generic product will be consistent with the codified tolerance when following the established withdrawal period.[56] As discussed in section F, your petition does not present any evidence or information that calls into question the human food safety of ractopamine as currently approved by FDA. The current

[53] NADA 141-221 Environmental Assessment for Cattle; FONSI dated 2000 https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFonsi/169

[54] NADA 141-290 – Environmental Assessment for turkeys dated 2001 (FONSI dated 2003), https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/803.

[55] NADA 141-290, FONSI dated 2003, https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadEA/803. "Based on worst-case scenarios, it does not appear that runoff from any combination of approved uses poses substantial risk to aquatic organisms. Low acute and chronic risk quotients for daphnids (the most sensitive aquatic species tested) indicate that the use of ractopamine hydrochloride within a single watershed is not likely to pose a substantial threat to aquatic organisms."

[56] If the generic sponsor proposes a different withdrawal period, it must show that the residues of the generic product at its proposed withdrawal period will be consistent with the established tolerance (512(n)(1)(A)(ii) of the FD&C Act).

tolerances were established in accordance with applicable law, and based on the information before FDA at this time, they are appropriate and adequate to protect public health. The approved tolerances ensure a reasonable certainty of no harm for the human consumer when the product is used as labeled.

III. Conclusion

For the reasons discussed above, pursuant to 21 CFR § 10.30, we granted your request to provide an opportunity for public comment on this petition and deny the remaining requests in your petitions.

Thank you for your interest in this matter.

Sincerely,

William T. Flynn -S Digitally signed by William T. Flynn -S
Date: 2025.02.28 06:41:49 -05'00'

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