April 29, 2025

Dockets Management Staff
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane (rm. 1-23, rm. 1061)
Rockville, MD 20852

PETITION FOR RECONSIDERATION

[Docket Nos. FDA-2012-P-1252; FDA-2020-P-1506]

Animal Legal Defense Fund ("ALDF"), Center for Food Safety ("CFS"), Food Animal Concerns Trust ("FACT"), and The Center for Biological Diversity ("the Center") (collectively, "Petitioners") submit this petition for reconsideration of the decision of the Commissioner of Food and Drugs in Docket Nos. FDA-2012-P-1252 and FDA-2020-P-1506.

A. Decision involved

This petition respectfully requests reconsideration of the U.S. Food and Drug Administration's ("FDA") February 28, 2025, denial of Petitioners' 2012 and 2020 citizen petitions.

B. Action requested

Pursuant to 21 C.F.R. § 10.33(b), Petitioners request that the Commissioner reconsider the petition denials and instead withdraw approval of ractopamine for use in pigs, cows, and turkeys or, alternatively, adopt stricter standards for its use.

C. Statement of grounds

1. Background

On December 20, 2012, ALDF and CFS submitted a citizen petition relating to the animal drug ractopamine. Specifically, the 2012 petition requested that FDA undertake the following actions: review the July 2012 Codex standards for ractopamine; publish the petition in the Federal Register and provide opportunity for comment; perform comprehensive scientific studies to characterize risks to animals, humans, and the environment posed by ractopamine use; and adopt more protective standards by, at a minimum, matching the Codex standards. On June 8, 2020, ALDF, FACT, and the Center submitted a related petition requesting immediate suspension of ractopamine's approval for pigs and cows based on the conditions created by the COVID-19 pandemic and, separately, withdrawal on the ground that the drug is unsafe. On December 17, 2020, FDA provided a partial response to the 2020 petition, denying suspension based on the pandemic conditions while noting that the request to withdraw approval for safety reasons remained under review, as did the 2012 petition.

On March 26, 2024, Petitioners initiated an unreasonable delay lawsuit by filing a complaint in the United States District Court for the District of Columbia seeking substantive responses to the 2012 and 2020 petitions. As a result of that lawsuit, the parties agreed to a deadline for a final response to both petitions. On February 28, 2025, FDA met that deadline and denied the 2012 petition (except as to the request to provide an opportunity for public comment) and denied the remainder of the 2020 petition.

2. Grounds for Reconsideration

a) FDA failed to engage with record evidence showing human food safety risks

In the 2025 Response, FDA glossed over the serious threats ractopamine poses to human safety. FDA stated that when it approved ractopamine, it "considered both acute and chronic exposure of people to residues of ractopamine in food," [2025 Response pp. 17-18] and "determined that the current tolerances for ractopamine meet the legal safety standard (i.e., reasonable certainty of no harm)." [*Id.*

p. 15] But the 2025 Response did not grapple with the evidence in the record that would frighten any meat consumer about health risks from exposure to ractopamine residues.

The 2020 Petition noted that FDA has long been aware that "humans with compromised cardiovascular systems react adversely to beta agonists." [2020 Petition pp. 10-11 (quoting July 19, 1995, Meeting Minutes Between Center for Veterinary Medicine and Hoechst-Roussel Agri-Vet Company)] Indeed, in 1995 FDA called for studies of acute toxicology "for beta agonists because of human sensitivity. . . . Tremors were seen in a human pilot study and, as such, [central nervous system] and cardiac effects should be studied." [July 19, 1995, Meeting Minutes Between Center for Veterinary Medicine and Hoechst-Roussel Agri-Vet Company] FDA noted that it was "very important" to obtain such studies. [*Id.*]

But as the 2020 Petition explained, FDA's consideration of the exposure of people to residues of ractopamine in food consisted of just one human study before FDA approved the drug:[1]

> Only one human study of ractopamine was attempted before FDA approved the drug; it started with a sample size of only six men, but one was removed from the study when he began experiencing an abnormally rapid heart rate. Indeed, the study was supposed to include escalating doses up to 65 and 100 mg, but "no subjects received the 65 or 100 mg dose" because "they were experiencing clinically significant heart rate increase at the 40 mg dose."

[2020 Petition p. 10 (quoting Clinical Report Overview IND 43, 991, Study T4V-LC-ERAA)] In other words, FDA shut down its sole study of humans from ractopamine exposures after one subject quit early on after his heart sped up after receiving a 25 mg dose, and the others suffered "clinically significant heart rate increase" at a 40 mg dose. Moreover, FDA and the applicant (Eli Lilly) agreed that the study would struggle to "determine a true no effect dose or evaluate safety unless a much larger

[1] The 2025 Response cited to an online "FOI summary" for "a significant body of data pertaining to human safety and ractopamine residues in food" [2025 Response p. 18 n.43], but the linked webpage does not work. Petitioners cannot access and evaluate whatever FDA linked. In addition, FDA supports its statement that it "considered acute and chronic exposure of people to" ractopamine residues with a sole citation to its Guidance for Industry #3—and does not identify the specific studies. [*Id.*p. 18 n.42]

sample size was used." [Clinical Report Overview IND 43, 991, Study T4V-LC-ERAA] Neither the 2020 Partial Response nor the 2025 Response demonstrated that such a larger human study happened.

Reviewing the six-person study, FDA's Medical Officer N. Stockbridge expressed serious concerns about ractopamine. The Medical Officer's Review first stated that "[a]t least partly because of the failure to explore higher doses, the dose-response function for all parameters was not well-studied." [Division of Cardio-Renal Drug Products, FDA, Medical Officer's Review, Jul. 28, 1998 (attached as n.54 to 2020 Petition)] Dr. Stockbridge noted that even with "the small number of subjects in this trial, cardiovascular effects were detectable with doses at or above 10 mg," expressed serious concerns with the low bioavailability of ractopamine and the uncertainty regarding what factors might affect it, reasoned that "a single dose study is not a reasonable basis upon which to estimate the no-effect level during chronic exposure," and concluded that "the data from this study do not provide adequate assurance that the expected ractopamine levels in meat products will be without cardiovascular pharmacological effects in man." [*Id.*]

The 2025 Response did not consider these previous FDA concerns about beta-agonists in general and ractopamine in particular, let alone explain why they are no longer applicable. Indeed, the 2025 Response acknowledged that there are at least two adverse drug event reports in humans that are consistent with FDA's previously expressed concerns: a person with a history of heart failure suffered heart problems after eating multiple meals of bacon; and a person suffered muscular issues after eating pork. [2025 Response p. 19] Moreover, in describing these two reports, FDA limited its response to the adverse drug events "you [i.e., Petitioners] reference" in the 2012 Petition [*id.*]—the agency does not appear to have considered all ractopamine adverse drug events for humans reported to it.[2]

---

[2] For example, the 2025 Response stated that FDA "monitors these reports to make decisions about product safety" but does not identify how many total adverse drug event reports for humans exist, how many of those come from oral exposure, and what types of events occur. [2025 Response p. 19]

Finally, the 2025 Response acknowledged that 168 other countries ban or restrict ractopamine but shockingly states that information is "not directly relevant." [2025 Response p. 16] While other countries' assessments of risks posed by ractopamine do not occur under the same legal framework as FDA's, they nonetheless show the widespread view that the drug is unsafe, or that the risks for allowing ractopamine at the levels FDA has set are too high. The 2025 Response attempted to minimize or distinguish the determinations by European Union, China, and Russia, but did not give the same consideration to the conclusions reached by scores of other countries. [*Id.* p. 16]

b) FDA's responses overlooked several key environmental risks

As FDA noted in the 2025 Response, the 2012 Petition "argue[d] that FDA has not completed an extensive review of the potential environmental effects of ractopamine." [2025 Response p. 20] While the 2012 Petition was pending, the 2020 Petition specifically expanded on these environmental risks, including, but not limited to:

- Ractopamine increases the risk of spreading pathogens—including antimicrobial-resistant pathogens—to workers and other humans in surrounding communities [2020 Petition pp. 8-9];
- Ractopamine risks harming humans through exposure pathways other than meat consumption, such as workers handling ractopamine who experience nausea, dizziness, headaches, nosebleeds, and respiratory, cardiac, and other health issues [*Id.* p. 9];
- Ractopamine excreted into wastewater or that is disposed of as uneaten medicated feed can enter into groundwater or other waterways and harm the environment; the 2020 Petition noted a study showing that typical levels of ractopamine found in wastewater can harm zebrafish [*Id*. pp. 11-12];
- Mass killing, or "depopulation," and subsequent burial of industrially farmed pigs and cows risks the leaching of ractopamine and other contaminants through the soil into groundwater and potentially other water bodies [*Id*. pp. 12-13].

The 2020 Partial Response did not respond at all to the first three bullet-pointed issues. The 2020 Partial Response did discuss carcass burial but created a straw man argument about "extralabel use." [2020 Partial Response p. 2] FDA asserted that ALDF, FACT, and the Center did not provide evidence "the depopulated animals had illegal ractopamine residues." [*Id.*] Yet the 2020 Petition was not so limited; it raised the issue that all pigs and cows given ractopamine who are killed en masse before slaughter and left to decompose in unlined trenches and pits could leach ractopamine into water bodies. [2020 Petition pp. 12-13]

Similarly, the 2025 Response did not directly respond to the above bullet-pointed issues. Instead, FDA referenced the Environmental Assessments that "the applicant" performed in 1995, 1998, and 2001, as well as FDA's review of the Environmental Assessments.[3] [2025 Response pp. 20-21] To the extent the 2025 Response touched on anything regarding the environmental issues described in the 2020 Petition, it noted toxicity assays on non-target organisms "have been conducted" and "did not reveal any adverse environmental effects." [*Id.* p. 21] But FDA did not identify who performed the assays, reference the studies, or otherwise explain any results or other details of the assays. And the non-target organisms that FDA listed as having assays performed did not include zebrafish.

In short, neither the 2020 Partial Response nor the 2025 Response adequately considered and responded to the environmental risks of ractopamine.

c) Proposed label changes will not adequately address demonstrated harms to pigs

In the 2025 Response, FDA acknowledged scientific data showing that ractopamine causes physical and psychological distress to pigs. Yet instead of banning or restricting its use, FDA has chosen to undertake voluntary label changes affirming "the need for the use of best practices in handling/management during transportation and marketing phases." [2025 Response p. 12] FDA reached this conclusion based on its review of a 2023 Elanco study, which was designed to resemble commercial conditions "during the marketing phase as closely as possible." [*Id.* p. 11] FDA noted that it believes "these handling methods are commonly used already." [*Id.* p. 12] Assuming these practices are already in place, it does not follow that labeling changes will address the agency-recognized harm to pigs fed ractopamine. Moreover, because FDA does not have the authority to require label changes,

[3] FDA linked these documents in the 2025 Response, but the web addresses do not work. [2025 Response p. 21 nn.50-51] As a result, Petitioners cannot evaluate the documents.

it must rely on voluntary compliance. FDA cannot ensure that drug manufacturers will make the requested changes, thus rendering its 2025 Response utterly toothless. FDA has in fact recognized this flaw in the statutory scheme itself, noting that "the current process for negotiating changes in labeling . . . result[s] in inconsistent practices and labeling information."[4] [FDA FY25 Legislative Proposals, *available at* https://www.fda.gov/media/176924/download (explaining that "FDA is proposing that the FD&C Act be amended to authorize the [CVM] to *require* animal drug sponsors to make safety-related labeling changes based on new safety information") (emphasis added)]

Moreover, FDA did not adequately consider that these mitigation measures will simply mask the problem while doing nothing to address the underlying physical and psychological stress suffered by pigs. FDA concluded that "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." [2025 Response p. 11] But the literature is not so limited. Petitioners cited numerous studies and sources demonstrating ractopamine's harmful impact on pigs independent of external conditions or exacerbating factors. These impacts include, but are not limited to:

- Psychological effects on pigs comparable to ecstasy and methamphetamine [2020 Petition p. 4 & n.14];
- Cardiovascular stress, muscular skeletal tremors, increased aggression, hyperactivity, acute toxicity, and genotoxicity [*Id*. p. 5 & n.19];
- Increase in aggression and hyperactivity, so much so that animals "must be medicated to calm them down for shipping to slaughter" [*Id.* p. 5 & n.20];
- Gait problems, reduction in bone mass and strength, inability to walk, broken limbs, and death [*Id*. p. 8].

FDA provided no reason for failing to engage with this evidence in its response.

[4] The "manageable risk approach" utilized by FDA makes little sense in this context. [2025 Response p. 3] While FDA claims that "congressional intent" militates against a zero risk approach, the only legislative material cited—a House Report accompanying a 1981 appropriations bill that briefly mentions subtherapeutic antibiotic use in animal feed—does not demand this standard. [*Id.* pg. 3 n.7] Given FDA's inability to ensure compliance with labeling changes and ractopamine's long-standing history of harm to animals, FDA should apply a zero risk standard here.

Additionally, FDA acknowledged that pigs fed ractopamine have an increased risk for hoof lesions and an inability to stand or walk. [2025 Response p. 11 (noting that the Post Approval Surveillance study "concluded that feeding ractopamine . . . can increase the number of non-ambulatory pigs," and explaining that literature "provided support that hoof lesions are more common in pigs fed ractopamine, which may lead to lameness.")] Changes in handling will not address these problems.

Finally, FDA noted that it "analyzed adverse drug events in swine fed ractopamine reported to CVM," which "included reports of death, recumbency, lethargy, lameness, and hyperactivity." [2025 Response p. 11] FDA specifically noted numerous reports of death where it was unable to rule out ractopamine as the cause. [*Id.*] Yet FDA offered no further analysis or context for these events nor any reason to discount the concern they raise. Moreover, FDA ignored adverse drug event reports cited by Petitioners identifying additional symptoms such as paralysis, severe redness of skin, immobility, vomiting, and rapid breathing, to name just a few. [2020 Petition p. 7]

In sum, FDA failed to adequately consider the diverse and substantial body of evidence demonstrating harm to pigs that will not be addressed by its proposed labeling changes.

d) Proposed label changes will not adequately address demonstrated harms to cows

FDA similarly acknowledged a variety of serious risks to cows fed ractopamine in the 2025 Response. Specifically, FDA discussed a study cited in the 2020 Petition (the "Loneragan" study) that showed an association between ractopamine use and death in cows. [2025 Response p. 13] Despite finding limitations with the study, FDA accepted that it "provides some evidence suggesting an increased mortality rate for cattle administered ractopamine." [*Id.*] FDA also noted adverse drug event reports of cow death where ractopamine could not be ruled out as the cause [*id.*], and "other potential risks associated with the use of ractopamine including anxiety, hyperactivity, and aggression," as well as decreased appetite. [*Id.* p. 14]

In response, FDA has chosen to "seek label changes to encourage use of best practices for handling/transport focused on minimizing stress." [2025 Response p. 14] But as previously discussed in regard to pigs, label changes relating to handling and transport do not address the underlying stress—both physical and psychological—that the drug itself wreaks on cows' bodies and minds. As Petitioners explained in the 2020 petition, the physiological reaction ractopamine creates in cows is "a permanent feeling of stress akin to how a human who has just woken up at the wheel of a car on the highway would feel." [2020 Petition p. 4] Better handling and transport will not address this harm at a base level. And this limited and attenuated response is particularly concerning given FDA's acknowledgment of evidence connecting ractopamine use to death.

FDA also failed to account for the full breadth of how ractopamine harms cows. Petitioners identified adverse event reports linking ractopamine to fever, lung congestion, pneumonia, and death by frothy bloat, to name just a few. [2020 Petition p. 7] Yet FDA limited its response to the above-mentioned risks (anxiety, hyperactivity, aggression, reduced appetite, and increased mortality rates) without explanation as to why it ignored the rest.

Additionally, FDA's response ignored the broader body of evidence cited by Petitioners that demonstrates the harm that beta-agonists, such as ractopamine, cause to cows. These include, but are not limited to:

- FDA scientists found beta-agonists linked to cardiomyopathy in cows [2020 Petition p. 4-5];
- FDA reports linking beta-agonists to fatal respiratory distress in cows [*Id.* p. 5];
- Studies connecting beta-agonists to "an increase in aggressiveness" and adverse effects "including hyperactivity, trembling, hoof loss, lameness, broken limbs, inability to walk, and fatigue syndrome." [*Id.* p. 6]

FDA offered no reason for its failure to consider this evidence.

Finally, FDA failed to consider gaps in its pharmacovigilance review and identify where additional studies may be needed. Although FDA took a close look at the Loneragan study, it ignored a 2006 Elanco study cited by Petitioners that found that cows "administered ractopamine were 90% more likely to die than control animals during the at-risk period." [2020 Petition p. 7] Importantly, despite acknowledging evidence that suggests an increased mortality rate for cows fed ractopamine, FDA did not seek out or perform further studies investigating this risk. As previously discussed, a 2023 Elanco study was central to FDA's response to ractopamine use in pigs. Yet FDA relied on no such recent study for cows.

In sum, FDA's proposed labeling changes do not address the risks it identified to cows and FDA failed to consider the numerous other risks identified by Petitioners.

e) Ractopamine's demonstrated harm to turkeys and its absence from the market for use in turkeys are reasons for FDA to withdraw approval

The 2025 Response stated both that adverse drug events "suggest a probable causal relationship between hyperactivity and hyperexcitability in turkeys administered ractopamine," and that "the drug has not been actively marketed for use in turkeys for almost a decade." [2025 Response p. 14] These two phenomena combined raise serious questions as to whether "there is a lack of substantial evidence that such drug will have the effect it purports or is represented to have," which is a basis for withdrawal. *See* 21 C.F.R. § 514.115(b)(3)(iii). At a minimum, FDA should consult with the sponsor as to whether the sponsor should request FDA withdraw approval of ractopamine for use in turkeys—an action that would take minimal agency resources. *See, e.g.*, 90 Fed. Reg. 6797 (Jan. 21, 2025) (withdrawing approval for DERMA-VET); 78 Fed. Reg. 78716 (Dec. 27, 2013) (withdrawing approval of five new animal drug applications for roxarsone oral dosage form products).

f) FDA does not have discretion to pursue labeling changes when an animal drug is unsafe

In the 2025 Response, FDA concluded that its resources were best used pursuing labeling changes, rather than withdrawal proceedings, because "the process of withdrawing approval of animal drugs requires significant time and agency resources." [2025 Response p. 15] FDA explained that "[b]y pursuing voluntary measures, CVM can address animal safety concerns without the time and expense of an adversarial process." [*Id.*] But, for the reasons discussed above, FDA's proposed voluntary label changes do not address the animal harms it acknowledged. Moreover, this response plainly applies only to "animal safety concerns," ignoring the human and environmental safety concerns identified by Petitioners.

FDA implied that it would have chosen this voluntary label change approach regardless of whether withdrawal was warranted. [2025 Response p. 15] But FDA does not have boundless discretion in this context. When "experience or scientific data" show that a drug is unsafe for use under its approved conditions, FDA has a mandatory duty to withdraw approval. 21 U.S.C. § 360b(e)(1)(A); *see Nat. Res. Def. Council, Inc. v. U.S. Food & Drug Admin.*, 760 F.3d 151, 172 (2d Cir. 2014) ("If the ultimate agency finding . . . is that the drug is not shown to be safe, the statute permits only one remedy—withdrawal of approval."). As previously discussed, FDA failed to adequately consider and address Petitioners' evidence that ractopamine is unsafe for animals, humans, and the environment. FDA's myopic review led it to a limited and inappropriate response. Had FDA given full weight and consideration to the entirety of Petitioners' evidence it would have been forced to conclude that ractopamine is unsafe, thus triggering a mandatory duty to act.

g) FDA is mistaken that it does not have the obligation and authority to review the Codex Standards for ractopamine and consider adopting them

The 2025 Response declined to review the Codex Standards for ractopamine, let alone consider adopting them or setting more stringent standards. [2025 Response pp. 5-6] FDA reasoned that "section 401 of the FD&C Act is inapplicable because MRLs are not definitions or standards of identity, quality, or fill of container," [*id.* at 5 n.10] and improperly narrowly construed 21 U.S.C. § 360b(a)(6) [*id.* at 6]. The agency's decision to ignore the Codex Standards is wrong; FDA's obligations to review Codex Standards are not limited to narrow, discrete instances of food standards that exclude standards for drug residues in meat and drugs mixed into animal feed.

First, the relevant regulatory provision calls for the review of all Codex "food standards," and does not limit FDA's review obligations to only Codex Standards the agency would issue pursuant to 21 U.S.C. § 341. *See* 21 C.F.R. § 130.6(a) ("All food standards adopted by the Codex Alimentarius

Commission will be reviewed by the Food and Drug Administration . . ."). Ractopamine residue limitations apply "in a specific edible tissue of a treated animal," *see* 21 C.F.R. § 556.570 (setting ractopamine "tolerances") and *id.* § 556.3 (defining tolerance), and "edible tissue" meets the plain meaning definition of "food." Moreover, the Food Drug & Cosmetic Act authorizes regulations that restrict food from containing "any poisonous or deleterious substance." 21 U.S.C. § 342. Standards setting a limitation of residues in "food" are clearly "food standards." The Codex Alimentarius Commission itself, on its website, recognizes that such limitations are "food standards." *See* Veterinary Drug Details, Ractopamine hydrochloride, Codex Alimentarius, https://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/vetdrugs/veterinary-drug-detail/en/?d_id=79 (last visited Apr. 23, 2025) (containing header "Codex Alimentarius: International Food Standards").

Even if FDA is right that it must only review standards authorized by 21 U.S.C. § 341, ractopamine residues in meat *do* fit within that authority. That statutory provision authorizes setting "standards for food" to include "a reasonable definition and standard of identity, *a reasonable standard of quality*, or reasonable standards of fill of container." 21 U.S.C. § 341 (emphasis added). Neither the act nor its regulations appear to define "standard of quality." Under a plain meaning reading, drug residues in meat tissue constitute a food "quality." *See "*Quality" definition, Merriam-Webster, https://www.merriam-webster.com/dictionary/quality (last visited Apr. 23, 2025) (defining "quality" as a "peculiar and essential character" or "a distinguishing attribute").

Third, the agency's past practice shows that it does not limit its Codex Standards review only to "regulations establishing standards of identity for food," as the 2025 Response suggested. [2025 Response p. 5] For example, "in accordance with 21 CFR 130.6," FDA reviewed "the Codex Alimentarius standard concerning reirradiation of foods." 51 Fed. Reg. 13376, 13393 (Apr. 18, 1986). Indeed, FDA has always viewed itself as having the authority to review and respond to Codex Standards for "Animal Food." Before 1999, FDA regulations included 21 C.F.R. part 564, titled "Definitions and Standards for Animal Food," which included a Codex review process with identical language to current 21 C.F.R. § 130.6. *See* 21 C.F.R. § 564.6 (1996). The agency withdrew part 564, but in doing so it stated, "FDA disagrees with comments that suggest removal of part 564 adversely affects the agency's authority to regulate animal food. . . . The act prohibits the sale of adulterated and misbranded food in interstate commerce. The definition of food relates to food for man or animal, i.e., feed. The act also allows the agency to establish standards of identity or standards of fill as needed." 64 Fed. Reg. 4293, 4294 (Jan. 28, 1999). This language shows that FDA has, for many decades until the 2025 Response, consistently and correctly viewed its regulation of "adulterated" food—including limits on drugs in food for man or animals—as "food standards" subject to the Codex Standards review process. Accordingly, the 2025 Response erred in ignoring the Codex Standards for ractopamine.

* * * *

For these reasons, Petitioners request that the Commissioner reconsider the petition denials and instead withdraw approval of ractopamine for use in pigs and cows and turkeys or, alternatively, adopt stricter standards for its use. Thank you for your consideration of this matter.

Respectfully submitted,

Maia Dunlap
Daniel Waltz
ANIMAL LEGAL DEFENSE FUND
611 Pennsylvania Ave SE #484
Washington, DC 20003
(707) 795-2533

On behalf of Petitioners Animal Legal Defense Fund, Center for Food Safety, Food Animal Concerns Trust, and Center for Biological Diversity