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**BEFORE THE COMMISSIONER OF  
THE UNITED STATES FOOD AND DRUG ADMINISTRATION**

**PETITION FOR EMERGENCY RULEMAKING**

Pursuant to the United States Constitution, the Administrative Procedure Act (“APA”),<sup>1</sup> the Federal Food, Drug, and Cosmetic Act,<sup>2</sup> and the Food and Drug Administration (“FDA”)’s implementing regulations,<sup>3</sup> the Animal Legal Defense Fund, Food Animal Concerns Trust, and the Center for Biological Diversity (collectively, “Petitioners”) submit this emergency petition requesting that the Commissioner immediately suspend the approval of ractopamine for use in pig and cattle feed under 21 C.F.R. § 558.500.

The Animal Legal Defense Fund (“ALDF”) is a national nonprofit membership organization based in California with over 200,000 members and supporters nationwide. ALDF’s mission is to protect the lives and advance the interests of animals through the legal system. Advocating for farmed animals is one of ALDF’s central goals. ALDF has long advocated for more responsible use of ractopamine in industrial animal production in the United States, but the need to restrict its rampant use among pigs and cows has become dire in light of the coronavirus pandemic and its significant disruption to meat supply chains.

Food Animal Concerns Trust (“FACT”) is a national nonprofit advocacy organization based in Illinois. FACT promotes the safe and humane production of meat, milk, and eggs. FACT envisions that all food-producing animals will be raised in a healthy and humane manner so that everyone will have access to safe and humanely produced food. FACT has long been concerned about both the human health impacts from the use of beta-agonist drugs like ractopamine and the impact on animal health and welfare.

The Center for Biological Diversity (“The Center”) is a non-profit environmental organization dedicated to the protection of native species and their habitats through science, policy, and environmental law. The Center has more than 1.7 million members and online activists dedicated to the protection and restoration of endangered species and wild places. For 26 years, the Center has worked to protect imperiled plants and wildlife, open space, air and water quality, and overall quality of life for people and animals from toxic threats such as pollution from industrial animal agriculture.

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<sup>1</sup> 5 U.S.C. § 553(e).

<sup>2</sup> 21 U.S.C. § 360b.

<sup>3</sup> 21 C.F.R. §§ 10.20, 10.30.

The novel coronavirus (“COVID-19”) pandemic has created a bottleneck at meatpacking plants and a national slowdown of slaughtering and processing animals for meat, which has led to animals remaining with producers and in transport for unexpected longer durations. As a result, animals normally fed ractopamine during the last few weeks of their lives receive the drug for longer durations, stay alive for longer periods after they receive the drug, or are “euthanized” (instead of slaughtered for food) with high amounts of ractopamine in their systems. This uncertainty of the timing for slaughtering or “euthanizing” animals fed ractopamine threatens animal safety and welfare, human health, and the environment. ALDF, FACT, and the Center now submit this emergency petition in order to protect the tens of millions of cows and pigs raised for food in the United States each year from needlessly suffering, to protect the health and safety of humans—as consumers and members of communities living adjacent to confined animal feeding operations (“CAFOs”) and slaughterhouses—and to protect the environment.

### **A. Requested Action**

Under the FDCA, FDA has the authority to suspend and withdraw approved animal drugs if such drugs present an “imminent hazard” or are shown to be unsafe.<sup>4</sup> ALDF requests that FDA use that authority to immediately suspend and/or withdraw the approval of ractopamine for use in pig and cow feed under 21 C.F.R. § 558.500.<sup>5</sup>

### **B. Statement of Grounds**

Because of the COVID-19 global pandemic and outbreaks at slaughterhouses throughout the United States, cows and pigs are now being held at CAFOs past the time at which they are typically sent to slaughter. Some of the largest cow and pig slaughterhouses in the country have been the source of COVID-19 outbreaks, with many shutting down operations temporarily or indefinitely.<sup>6</sup> At certain points of the past two months, the country’s pig slaughter and processing

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<sup>4</sup> Proposed Rulemaking, Proposed Statement of Interpretation and Policy regarding Imminent Hazard to the Public Health, 35 Fed. Reg. 18679 (Dec. 9, 1970).

<sup>5</sup> This petition uses “pigs” and “cows” to refer to the animals identified as “swine” and “cattle” in Section 558.500’s approved “Conditions of use” provisions. *See* 21 C.F.R. § 558.500(e)(1)-(2), (4).

<sup>6</sup> Google Maps Map of North American Meat Plant Locations Where the Companies Have Reported COVID-19 Positives, at [https://www.google.com/maps/d/viewer?hl=en&ll=42.957440018435214%2C-87.86539885849584&z=15&mid=1vpbLCKW\\_gW0DiUVg\\_n7lZ-gLeBUWqqiD](https://www.google.com/maps/d/viewer?hl=en&ll=42.957440018435214%2C-87.86539885849584&z=15&mid=1vpbLCKW_gW0DiUVg_n7lZ-gLeBUWqqiD) (last visited May 27, 2020).

facilities were operating at only 50-60% of their capacity.<sup>7</sup> As facilities reopen, there is still significant backlog in the supply chain that will last into the foreseeable future.<sup>8</sup>

CAFO operators are now faced with two choices: hold animals on the premises indefinitely, until they can be sent to the slaughterhouse; or kill them and dispose of their bodies, typically on site. The use of ractopamine greatly exacerbates the risks of either option to animals, handlers, public health, and the environment.

In a nutshell, because producers administer pigs and cows ractopamine at levels that cause them to rapidly deteriorate both physically and behaviorally, the additional time spent on the drugs waiting at CAFOs results in significant suffering and impairments that will increase the likelihood of them suffering at CAFOs and being mistreated during handling on their way to slaughter. The slaughterhouse slowdowns and bottlenecks will increase the incidence and ways in which the animals' bodies tear, crack, and fall apart. The cows and pigs will also receive more ractopamine than in the usual course of business, which will result in increased drug residues in cow and pig products entering the food supply. Pigs and cows who are killed on the CAFO or somewhere during transportation without making it to slaughter at the slaughterhouse are often disposed of in mass graves or by other means on-site, thereby increasing the risk that ractopamine residues will contaminate local water and other environmental media.

The continued use of ractopamine during the COVID-19 pandemic thus presents an imminent hazard to animal and human health and the environment. Moreover, in the current conditions ractopamine is not shown to be safe for use. The FDA must take action.

### *Ractopamine's Use*

Ractopamine belongs to a class of drugs called beta-agonists, which are widely used in meat production in the United States due to their efficacy in increasing animal growth. Beta-agonists shift dietary energy balance toward skeletal muscle growth as opposed to fat deposition. Producers often feed beta-agonists to animals during the “finishing” stage of growth—the final period of weight gain before slaughter—to encourage a last-minute increase in muscle mass and

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<sup>7</sup> Dylan Matthews, *The closure of meatpacking plants will lead to the overcrowding of animals. The implications are horrible.*, Vox, May 4, 2020, available at <https://www.vox.com/2020/5/4/21243636/meat-packing-plant-supply-chain-animals-killed>; see also Greg Cima, *Slaughter delays lead to depopulation*, JAVMA News, May 28, 2020, available at <https://www.avma.org/javma-news/2020-06-15/slaughter-delays-lead-depopulation> (citing USDA Agricultural Marketing Service data from May 9, 2020, to explain that “cattle slaughter that week was down 32% from a year earlier, and swine slaughter declined 24%,” and USDA Economic Research Service analysis on May 18 to explain that “[p]ork production fell 11% [and] beef production fell 21% . . . when looking at federally inspected production in April compared with a year earlier”).

<sup>8</sup> Mike Dorning, *Meat Plants to Reopen in 'Days Not Weeks,' USDA Boss Says*, Apr. 30, 2020, available at <https://www.bloomberg.com/news/articles/2020-04-30/meat-plants-to-reopen-days-not-weeks-under-trump-order-perdue>; see also Cima, *Slaughter delays lead to depopulation* (citing Minnesota's state veterinarian for the data point that on April 30, 2020, the JBS slaughter plant workers in Worthington, Minnesota were “euthanizing” thousands of pigs instead of slaughtering them for processing); *id.* (reporting that Tyson reported in an investor call that it believed U.S. pig processing capacity “had declined by half”).

overall carcass weight of the animals, which allows producers to receive more money per animal. Available research, including in FDA’s own files, shows that beta-agonists have substantial negative impacts on animal health, human health, and the environment.

FDA approved the use of ractopamine for pigs in 1999, for cows in 2003, and for turkeys in 2008. It is marketed as “Paylean” for pigs, “Optaflexx” and “Heifermax” for cows, and “Topmax” for turkeys. It is widely used in U.S. meat production; for pigs alone, around 60-80% of those raised for food in the United States receive the drug,<sup>9</sup> amounting to tens of millions of animals each year. Ractopamine is so pervasive because of the economic benefits of increasing animal growth at the end of an animal’s life while giving them less feed.<sup>10</sup> Indeed, it is specifically approved for these uses.<sup>11</sup> Estimates conclude that it allows producers to increase their profits by as much as \$2 per animal<sup>12</sup> by fueling a last-minute increase in an animal’s muscle mass, which then increases the carcass weight (and therefore dollar value) of the animal.<sup>13</sup> But as shown below, there are serious animal welfare and human health concerns with the drug remaining in the animals’ bodies until the moment they die—from slaughter or from other means. Ractopamine is therefore approved for use during a specified period, but with a withdrawal period occurring a few days before an animal is slaughtered.

### *Ractopamine’s Effects on Animals*

In addition to creating a rapid increase in muscle mass, ractopamine causes severe physical and psychological harm to the animal receiving it. Target animals administered the drug suffer from tremors, hoof deterioration and destruction, and heart problems. The drug also creates a physiological reaction in pigs and cows that is as 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. Indeed, one peer-reviewed study found that ractopamine is a “full agonist of MTAAR1,” meaning that it has the psychological effect of ecstasy and methamphetamine on cows, pigs, and turkeys.<sup>14</sup>

Beta-agonists induce increased heartbeat, relaxation of blood vessels and muscle, and contraction of cardiac tissue. FDA scientists have found that beta-agonists are linked to cardiomyopathy in cows, a disease of the heart muscle that makes it harder for the heart to pump

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<sup>9</sup> Helena Bottemiller, *Dispute over Drug in Feed Limiting US Meat Exports*, NBCNEWS.com, January 25, 2012, available at: <http://www.nbcnews.com/business/dispute-over-drug-feed-limiting-us-meat-exports-174014> [“Bottemiller, *Dispute over Drug in Feed*”].

<sup>10</sup> J.P. Wang et al., *Technical Note: A Monoclonal Antibody-Based Immunoassay for Determination of Ractopamine in Swine Feeds*, 84 J. Animal Sci. 1248 (2006); 21 C.F.R. § 558.500(e)(1)(i); 21 C.F.R. § 558.680(e)(1).

<sup>11</sup> 21 C.F.R. § 558.500(e)(1)(i); 21 C.F.R. § 558.680(e)(1).

<sup>12</sup> Bottemiller, *Dispute over Drug in Feed*.

<sup>13</sup> 21 C.F.R. § 558.500(e)(1)(i); 21 C.F.R. § 558.680(e)(1).

<sup>14</sup> 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). Methamphetamine can interrupt dopamine uptake via its interaction with TAAR1—in other words, cells are deprived of dopamine—which can lead to a variety of diseases and negative conditions.

blood to the rest of the body, and other “adverse effects” on the heart.<sup>15</sup> FDA is also aware that beta-agonists are linked to fatal respiratory distress in cows, which often occurs in conjunction with heat stress, overheating, or dust inhalation due to dry conditions.<sup>16</sup> One study, looking at a wide array of feedlot data, discovered that “deaths attributable to [beta-agonist] administration among those cattle in the exposed cohort, varied little from dataset to dataset, remaining relatively constant at 40-50%.”<sup>17</sup>

Existing studies show that ractopamine mimics stress hormones, increasing heart rate and relaxing blood vessels,<sup>18</sup> and is linked to significant health problems and behavioral changes in animals, such as cardiovascular stress, muscular skeletal tremors, increased aggression, hyperactivity, acute toxicity, and genotoxicity.<sup>19</sup> Highly-stressed animals exhibit behavioral problems and have difficulty socializing with other animals, resulting in more social hierarchy issues and fights within a flock or herd. Some reports indicate animals on ractopamine become so aggressive and hyperactive that they must be medicated to calm them down for shipping to slaughter.<sup>20</sup>

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<sup>15</sup> Apr. 23, 1999 Letter from Louis Mulligan, Ph.D, to Hoechst Roussel Vet regarding INAD submission and accompanying submission (noting study of zilpaterol hydrochloride found an increased heart weight in rats at doses of all levels).

<sup>16</sup> FDA, Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Reports (describing adverse reactions including, *inter alia*, “unusual hoof loss in cattle being fed the beta agonist Zilmax); *see also* FDA/CVM – ADE Reports, Prepared 8/19/2013 (compilation of some adverse drug experience reports for zilpaterol).

<sup>17</sup> G.H. Loneragan et al., *Increased Mortality in Groups of Cattle Administered the B-Adrenergic Agonists Ractopamine Hydrochloride and Zilpaterol Hydrochloride*, 9 Plos One e91177 (2014).

<sup>18</sup> Bottemiller, *Dispute over Drug in Feed*.

<sup>19</sup> R. Poletto et al., *Aggressiveness and Brain Amine Concentration in Dominant and Subordinate Finishing Pigs Fed the  $\beta$ -Adrenoreceptor Agonist Ractopamine*, 88 J. Animal Sci. 3107 (2010), available at: <http://www.animal-science.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. Animal Sci. 1184 (2009), available at: <http://www.animal-science.org/content/88/3/1184.full.pdf>; Ctr. for Food Safety, *America’s Secret Animal Drug Problem: How lack of transparency is endangered human health and animal welfare*, 3-4 (Sept. 2015) (citing sources showing pigs taking ractopamine were reported to have suffered adverse effects—hyperactivity, trembling, broken limbs, inability to walk and death) [“CFS, America’s Secret Animal Drug Problem”]; 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 165 (2004) (abstract that “pigs fed Paylean are more susceptible to stress when handled aggressively, compared with pigs not fed Paylean” and take longer to return to normal) [“James et al. (2004)”]; *see also, e.g.*, Ctr. Veterinary Medicine, FDA, *Adverse Drug Effects Comprehensive Clinical Detail Listing 1/1/1987 thru 3/31/2011, Drug Listing: N thru S* 177-84, at: <http://web.archive.org/web/20110426003851/http://www.fda.gov/downloads/AnimalVeterinary/SafetyHealth/ProductSafetyInformation/UCM055411.pdf> (last visited Dec. 17, 2012) (listing adverse drug effects for horses, pigs, cattle, turkeys, dogs, and humans).

<sup>20</sup> *See, e.g.*, D. Courtheyn et al., *Recent Developments in the Use and Abuse of Growth Promoters*, 473 Analytic Chimica Acta 71 (2002).

Scientists have also linked beta-agonists to a number of behavioral changes in animals that correspond to the physiological effects of the drug, including an increase in aggressiveness and a variety of adverse drug effects including hyperactivity, trembling, hoof loss, lameness, broken limbs, inability to walk, and fatigue syndrome.<sup>21</sup> These conditions make animals more difficult to handle, increasing the incidence of violence towards animals by handlers at CAFOs and slaughterhouses, while also increasing the potential for handlers to be injured. Because beta-agonists negatively influence animal welfare and behavior, their use corresponds to an increased risk to humans who work with them. Indeed, the beta-agonist Zilpaterol was voluntarily withdrawn by its drug sponsor, Merck, because slaughterhouses throughout the United States reported concerns about non-ambulatory, slow, and difficult-to-move cows, and cows with severely deteriorated hooves.<sup>22</sup>

Ractopamine's added risks of injury to workers who must handle behaviorally stressed and non-ambulatory pigs and cows is unjustifiable during the COVID-19 pandemic. Workers in industrial animal agriculture generally, and slaughterhouses in particular, are working in perilous conditions because of the virus and meat companies' unwillingness to provide a safe working environment. Indeed, the slaughterhouse and processing plant bottlenecks are the result of unsafe workplace conditions—unprotected workers standing shoulder to shoulder and coerced to work while sick have suffered the wrath of a highly contagious virus, forcing many plants to close.<sup>23</sup>

FDA itself has overwhelming evidence that ractopamine creates stress, non-ambulatory, and other adverse effects pigs, cows, turkeys, chickens, dogs, and other animals.<sup>24</sup> Ractopamine has been the basis of more reports from producers and researchers to FDA of sickened or dead

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<sup>21</sup> Ron Clarke, *What we know about Fatigued Cattle Syndrome: Vet Advice with Dr. Ron Clarke*, Canadian Cattlemen: The Beef Magazine, Dec. 7, 2018, available at <https://www.canadiancattlemen.ca/vet-advice/what-we-know-about-fatigued-cattle-syndrome/>.

<sup>22</sup> See, e.g., Huffstutter & Polansek, *Special Report: Lost hooves, dead cattle before Merck halted Zilmax sales*, Reuters, Dec. 30, 2013, available at: <https://www.reuters.com/article/us-zilmax-merck-cattle-special-report/special-report-lost-hooves-dead-cattle-before-merck-halted-zilmax-sales-idUSBRE9BT0NV20131230> (describing how one expert saw that “the animals’ hooves were ‘basically coming apart’” after being administered the drug and transported in hot temperatures).

<sup>23</sup> Michel Corkery & David Yaffe-Bellany, *The Food Chain's Weakest Link: Slaughterhouses*, The New York Times, Apr. 18, 2020, available at <https://www.nytimes.com/2020/04/18/business/coronavirus-meat-slaughterhouses.html>; Tom Polansek, *Coronavirus forces Tyson Foods to shutter two major U.S. pork plants*, Reuters, Apr. 22, 2020, available at <https://www.reuters.com/article/us-health-coronavirus-tyson-foods/coronavirus-forces-tyson-foods-to-shutter-two-major-u-s-pork-plants-idUSKCN2241ZV>; Natalia V. Navarro, *State Closes JBS Meatpacking Plant For At Least Two Weeks While Workers Are Tested For COVID-19*, Colo. Public Radio, Apr. 13, 2020, available at <https://www.cpr.org/2020/04/13/state-closes-jbs-meatpacking-plant-for-at-least-two-weeks-while-workers-are-tested-for-covid-19/>.

<sup>24</sup> See Eric S. Dubbin, DVM, Veterinary Medical Review, I-6557 (P-0141); Elanco, 91 Animal Health, a Division of Eli Lilly and Company, Optaflexx Annual, Drug Experience Report, NADA 141-221, p. 13 (describing heart problems in greyhounds administered ractopamine); Paylean Annual Periodic Drug Experience Report, NADA 140-863, 356.

pigs than any other drug given to pigs<sup>25</sup>; FDA's data demonstrates more pigs have experienced adverse effects from ractopamine than any other veterinary drug.<sup>26</sup> Studies and practical use have resulted in findings including:

- Of a group of 308 pigs given ractopamine, 91 became recumbent, ataxic, and dyspneic after arriving at the slaughterhouse from a finishing feedlot.<sup>27</sup>
- The incidence of death among cows administered beta-agonists was 75-90% greater than cows not administered these drugs.<sup>28</sup>
- Cows administered ractopamine were 90% more likely to die than control animals during the at-risk period.<sup>29</sup>
- In another instance, 56 out of 2000 pigs fed ractopamine died and 39 more were non-ambulatory.<sup>30</sup>

Adverse reactions to the drug in animals also include leg stiffness, paralysis, immobility, rapid breathing, severe redness of the skin, muscle tremors, walking with difficulty,<sup>31</sup> frequent vomiting, decreased motor activity, lacrimation, vasodilation affecting ears and abdomen,<sup>32</sup> fever, bloody diarrhea, enlarged lymph nodes, cracked hooves, coughing, lung congestion, infections on the body,<sup>33</sup> cannibalism, heart attack, aortic rupture, increased fighting, hyperactivity,<sup>34</sup> high body temperature, pneumonia,<sup>35</sup> aggressive sexual behavior, death by frothy bloat and other means,<sup>36</sup> to

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<sup>25</sup> *Id.*; see also Bottemiller, *Codex Adopts Ractopamine Limits for Beef and Pork*, Food Safety News (July 6, 2012), available at: <http://www.foodsafetynews.com/2012/07/codex-votes-69-67-to-advance-Ractopamine-limits-for-beef-and-pork/#.UM-yaKX758s>; Helena Bottemiller, *Ractopamine and Pigs: Looking at the Numbers*, Food & Env't Reporting Network (Feb. 23, 2012), available at: <http://thefern.org/2012/02/Ractopamine-and-pigs-looking-at-the-numbers/> (noting the next highest number after 218,116 pigs negatively affected by Ractopamine was significantly lower: 32,738 pigs negatively affected by Tylosin) [*Bottemiller, Ractopamine and Pigs: Looking at the Numbers*"].

<sup>26</sup> Bottemiller, *Ractopamine and Pigs: Looking at the Numbers*.

<sup>27</sup> Dec. 6, 2000, Adverse Drug Experience Report submitted to FDA.

<sup>28</sup> Loneragan et al. (2014).

<sup>29</sup> Elanco Animal Health, Post Registration Study – Epidemiological Characterization of Mortality Risk Associated With Administration of Optaflexx in Feedlot Cattle, Study No. T4VAM0512 (circulated May 18, 2006).

<sup>30</sup> Oct. 1, 2002, Adverse Drug Experience Report submitted to FDA.

<sup>31</sup> Sept. 20, 2002, Adverse Drug Experience Report submitted to FDA.

<sup>32</sup> Adverse Drug Experiences on file with Center for Veterinary Medicine, FDA.

<sup>33</sup> FDA, Summary of study trials of ractopamine hydrochloride effects on cattle, NADA 141-221.

<sup>34</sup> Excerpts of FDA/CVM Adverse Drug Experience Reports.

<sup>35</sup> Necropsy Reports on file with Center for Veterinary Medicine.

<sup>36</sup> Excerpts of FDA/CVM Adverse Drug Experience Reports.

name a few. Pigs given ractopamine have also produced stillborn piglets and piglets who died a short time after delivery.<sup>37</sup>

Ractopamine also increases numbers of “downer” or lame animals, associated with a complete inability to walk, broken limbs, and death.<sup>38</sup> “Downer” pigs also have increased cortisol levels, which may result from experiencing stress caused by illness, trauma, or environmental changes.<sup>39</sup> Research has demonstrated that among pigs in similarly stressful conditions, those fed Paylean had further elevated cortisol levels, leading to increased blood glucose concentrations.<sup>40</sup> Studies have also found that ractopamine can reduce bone mass and bone strength, such that a heavier pig is held up by weaker bones—likely affecting lameness, injuries, and increased prevalence of downers.<sup>41</sup> According to one study by the biotech industry and university researchers that evaluated the effects of ractopamine on pigs, “[t]he occurrence of downer pigs may be amplified by the industry trend of producing a more heavily muscled, lean genotype pig.”<sup>42</sup> Moreover, in one study that fed Paylean to a group of pigs, and compared the effects of transport with a control group of pigs not fed Paylean, scientists found “pigs fed diets containing Paylean were more susceptible to adverse effects on metabolic parameters when handled ‘roughly’ (prodded with electric shocks) than were pigs fed diets without Paylean.”<sup>43</sup>

#### *Ractopamine’s Effects on Human Health*

Because the use of beta-agonists in animals increases the likelihood that they will suffer from conditions that cause them to collapse before slaughter, there are increased food safety risks with consuming products derived from them. Cows and pigs raised for food in industrial facilities already suffer from stress due to their living conditions and physical abuse. Stress depresses the immune system, making animals more susceptible to pathogens, and increases animals’ susceptibility to and shedding of zoonotic bacteria such as *salmonella*. “Downer” animals who collapse into the dirt are further exposed to pathogens on the ground, which they then carry into the slaughterhouse. These additional contamination pathways expose consumers to increased health risks. Ractopamine has also been shown through studies to increase *salmonella* in cow feces; in one study, the percentage of animals shedding *salmonella* in their feces tended to be

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<sup>37</sup> Reaction Data submitted to FDA by Elanco Animal Health.

<sup>38</sup> CFS, *America’s Secret Animal Drug Problem*; James et al. (2004) (stating in abstract that “pigs fed Paylean are more susceptible to stress when handled aggressively, compared with pigs not fed Paylean” and take longer to return to normal); 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) (stating that animals on Ractopamine have increased gait problems and behavioral reactivity and spend more time lying and less time walking).

<sup>39</sup> James et al. (2004), *supra* n.19.

<sup>40</sup> *Id.*

<sup>41</sup> See M.J. Ritter et al., *Review: Effects of Ractopamine Hydrochloride (Paylean) on welfare indicators for market weight pigs*, 1 Transl. Anim. Sci. 533, 540 (2017).

<sup>42</sup> James et al. (2004), *supra* n.19.

<sup>43</sup> *Id.*



higher among those animals fed ractopamine than the control group.<sup>44</sup> In addition, studies have shown that antibiotic resistant bacteria, which can include salmonella, can jump from confined cows and pigs to workers and humans in neighboring communities.<sup>45</sup> Thus, because beta-agonists negatively influence cows' and pigs' behavior, leading to increased risk of infection and antibiotic resistance, their use corresponds to an increased risk to humans who work at or live near CAFOs and slaughterhouses and who eat products made from these animals.

FDA is also aware that beta-agonist exposure has been linked to adverse reactions in workers and producers in the animal agriculture industry, and residues in meat have also been reported to harm consumers. FDA has received numerous complaints from workers and consumers who experienced nausea, dizziness, headaches, fever, nose bleeds, respiratory issues and chest pain, allergic reactions, cardiac issues such as irregular heartbeat and rapid heartbeat, and other serious medical conditions requiring treatment and hospitalization, all after either being directly exposed to or consuming meat from animals fed beta-agonists.<sup>46,47</sup>

As Consumers Union found in 2012, ractopamine residues are widely present in our food supply: residual amounts of the drug were found in about one-fifth of the samples tested.<sup>48</sup> Studies have also recognized “there is a possibility that adulteration of feed with ractopamine could result in residues in animal tissues and lead to human poisoning.”<sup>49</sup> For example, the Sichuan Pork Trade Chamber of Commerce in China estimates that between 1998 and 2010, 1,700 people were poisoned from eating pigs fed Paylean.<sup>50</sup>

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<sup>44</sup> T.S. Edrington et al., *Effects of Ractopamine HCl on Escherichia Coli O157:H7 and Salmonella in Vitro and on Intestinal Populations and Fecal Shedding in Experimentally Infected Sheep and Pigs*, 53 *Curr. Microbiol.* 82 (Jul. 2006).

<sup>45</sup> M. Carrel et al., *Residential Proximity to Large Numbers of Swine in Feeding Operations Is Associated with Increased Risk of Methicillin-Resistant Staphylococcus aureus Colonization at Time of Hospital Admission in Rural Iowa Veterans*, 35 *Infection Control & Hosp. Epidemiology* 190 (2014) (jump to vulnerable Iowa residents); J.A. Casey et al., *High-Density Livestock Operations, Crop Field Application of Manure, and Risk of Community-Associated Methicillin-Resistant Staphylococcus aureus Infection in Pennsylvania*, 21 *JAMA Intern Med.* 1980 (Sept. 2013) (elevated rates of infection in study of nearly 450,000 Pennsylvania residents).

<sup>46</sup> Sept. 24, 2013 Veterinary Adverse Drug Reaction, Lack of Effectiveness, Product Defect Report for Zilmax (describing human worker experiencing “chemical pneumonia” and consequent permanent lung and heart damage because of inhalation of zilpaterol added to feed bin); Excerpts of Adverse Drug Experience Reports regarding human exposure to ractopamine (including, *inter alia*, nosebleeds, headaches, and fevers after inhaling the drug).

<sup>47</sup> Ctr. Veterinary Medicine, FDA, CVM ADE Comprehensive Clinical Detail Listing (1987-2011) (compiling statistics of adverse drug reactions, including in humans).

<sup>48</sup> Consumers Union, *Consumer Reports Investigation of Pork Products Finds Potentially Harmful Bacteria Most of Which Show Resistance to Important Antibiotics*, Press Release (Nov. 27, 2012), available at: <http://pressroom.consumerreports.org/pressroom/2012/11/my-entry-4.html>.

<sup>49</sup> Wang et al. (2006), *supra* n.10.

<sup>50</sup> 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, Feb. 2, 2010, available at:

FDA scientists have long expressed concern about the human health effects of ractopamine, dating back to FDA's approval of the drug without even one complete human study. Butopamine, the RR stereoisomer of ractopamine, had been considered as a human therapeutic during the 1970s, but research was discontinued due to severe cardiac side effects, including tachycardia.<sup>51</sup> 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.<sup>52</sup> 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."<sup>53</sup> The Medical Officer Review by FDA's Division of Cardio-Renal Drug Products of this lone human study expressed concern about the low bioavailability of the drug, and that dietary or constitutional variables could result in an increase in bioavailability, which could increase dose-response by one log unit. In other words, it is still not known if consuming ractopamine residues in food at the same time as other foods would make it more readily absorbed by a consumer, which could easily make it ten times stronger.<sup>54</sup> FDA also noted "repetitive dosing at reasonable intervals for meals will likely show cumulative effects, and likely show that doses of 5 mg or less per day in divided doses would produce cardiovascular effects."<sup>55</sup> As a result, FDA's *own* Medical Officer Review concluded: "In summary, 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."<sup>56</sup> This concern takes on added significance when, thanks to the disruption to slaughtering and processing facilities, animals receive extended durations of ractopamine or shorter withdrawal periods (and, as a result, increased ractopamine residues in the produced meat).

FDA scientists have further observed that beta-agonists' "[e]ffects are not desirable for consumers of food containing residues of the drug."<sup>57</sup> FDA scientists are also aware that humans

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[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](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).

<sup>51</sup> M.J. Thompson et al., *Hemodynamic effects of intravenous butopamine in congestive heart failure*, 28 *Clinical Pharmacology and Therapeutics* 324-334 (1980).

<sup>52</sup> Bottemiller, *Dispute over Drug in Feed*; see also EFSA Safety Evaluation of Ractopamine at 19 ("Subject 5 was withdrawn from the study before receiving the 40 mg dose of ractopamine because of adverse events (sensation of an increase in heart rate and sensation of heart pounding).")

<sup>53</sup> Clinical Report Overview IND 43, 991, Study T4V-LC-ERAA.

<sup>54</sup> See Division of Cardio-Renal Drug Products, FDA, Medical Officer's Review at 10 (review of N. Stockbridge, M.D., Ph.D). As of the date of the filing of this petition, Dr. Stockbridge is the Director of the Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiovascular and Nephrology.

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

<sup>57</sup> Apr. 23, 1999 Mulligan Letter & accompanying submission, *supra* n.15.

with compromised cardiovascular systems react adversely to beta-agonists,<sup>58</sup> and in fact has encouraged beta-agonist drug sponsors to study cardiac issues in beta-agonist studies after tremors were seen in a pilot study.<sup>59</sup>

Indeed, beta-agonists are banned or restricted in many other countries because of human safety concerns. All European Union members, China, Japan, South Korea, and Russia are some of the 168 countries that prohibit or restrict ractopamine in pig production.<sup>60</sup> The European Food Safety Authority panel banned the drug in part because its data could not support a conclusion that the drug is safe.

#### *Ractopamine's Effects on the Environment*

Finally, beta-agonists also harm the environment. Animals excrete approximately 95% of the ractopamine they ingest in the first three days after consumption,<sup>61</sup> which then contaminates ground and surface waters when manure lagoons leak or land-applied manure runs off the land into waterways. Uneaten medicated animal feed can also be buried in the ground at CAFOs, further leaching the drugs into the environment. These discharges degrade water quality both for recreation and drinking water. Indeed, Elanco, the manufacturer of Optaflexx, Paylean, and Topmax, acknowledges that ractopamine may leach “into the soil and groundwater from confinement areas . . . and runoff from land fertilized with manure from treated animals,” and acknowledges that this will potentially alter the chemical composition of those waterways. The discharges also harm wildlife—even at typical levels of ractopamine found in wastewater.<sup>62</sup> Elanco has stated in its Material Safety Data Sheet for ractopamine that the drug is moderately toxic to plants and slightly toxic to aquatic invertebrates. A 2010 study of veterinary

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<sup>58</sup> July 19, 1995 Meeting Minutes for Meeting Between Center for Veterinary Medicine and Hoechst-Roussel Agri-Vet Company.

<sup>59</sup> *Id.*

<sup>60</sup> Indeed, Russian scientists published a study in 2014 modeling the expected risk of cardiovascular system disorders caused by ractopamine residues in meat (at levels allowed by the Codex Alimentarius Commission), which concluded that the risk of life expectancy decrease from additional cases of cardiovascular diseases from ractopamine usage were unacceptable. See N.V. Zaitseva et al., *Health Risk Assessment of Exposure to Ractopamine Through Consumption of Meat Products*, 2 Int'l J. of Advanced Research 538 (Sept. 2014).

<sup>61</sup> Scientific Opinion of the Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) on a request from the European Commission on the safety evaluation of Ractopamine. 1041 The European Food Safety Authority Journal. (2009).

<sup>62</sup> A. Sachett et al., *Ractopamine hydrochloride induces behavioral alterations and oxidative status imbalance in zebrafish*, J. Toxicology & Envtl. Health, Pt. A (Feb. 2018) (finding that exposure to ractopamine at levels typically found in CAFO wastewater released into the environment induced behavioral alterations and oxidative stress in zebrafish”). Other studies have found ractopamine exposure causing endocrine-disrupting effects in fish and organ damage and altered lifespans in other species. *Id.* at 2 (collecting literature).

pharmaceuticals in groundwater near livestock operations detected ractopamine in water samples from pig facilities.<sup>63</sup>

In addition to the high prevalence of the drug itself in animal wastes, manure from animals fed ractopamine ultimately has higher levels of nitrogen, phosphorous, and sulfur, which contributes to ecosystem-disrupting nutrient pollution when the waste runs off into local waterways.<sup>64</sup> Thus, suspending or withdrawing the drug will have environmental co-benefits of reduced nutrient pollution in water bodies.

Environmental degradation is especially a threat during the COVID-19 pandemic because producers are responding to slaughterhouse and processing plant bottlenecks by “depopulating” entire herds on-site at CAFOs— *i.e.*, performing mass killings of pigs and cows.<sup>65</sup> After killing the animals, producers then carry the exterminated pigs by bulldozer out of the CAFO buildings and bury them.<sup>66</sup> The scale of the ongoing mass extermination and burial of pigs and cows is enormous; according to the industry’s trade group, producers will need to depopulate approximately 700,000 pigs per week.<sup>67</sup> The mass burials of pigs and cows with bodies full of ractopamine risks that the dead animals’ decomposition will add to the contribution of ractopamine into groundwater and potentially surface water bodies.

On-site burial of dead carcasses in unlined trenches and pits (as is occurring throughout the country during the pandemic) poses significant risks to the environment and public health.<sup>68</sup> Burial

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<sup>63</sup> S. Bartelt-Hunt et al., *Occurrence of Steroid Hormones and Antibiotics in Groundwater Impacted by Livestock Waste Control Facilities*, 123 J. Contam. Hydrol. 94 (April 2011).

<sup>64</sup> P.H. Watanabe et al. *Manure production and mineral excretion in feces of gilts fed Ractopamine*, 35 Acta Scientiarum. Animal Sciences 267 (July-Sept. 2013).

<sup>65</sup> Glenn Greenwald, *Hidden Video and Whistleblower Reveal Gruesome Mass-Extermination Method for Iowa Pigs Amid Pandemic*, The Intercept, May 29, 2020 (describing the investigation at Iowa Select Farms that showed the corporate producer turning off the ventilation fans and turning up the heat, causing the pigs to have “sustained screams of distress and agony” before they die). The link for this article, which includes video footage of the mass killing, is located at <https://theintercept.com/2020/05/29/pigs-factory-farms-ventilation-shutdown-coronavirus/>.

<sup>66</sup> *Id.* (noting that because the method of depopulation does not have a 100% mortality rate, some pigs may end up buried alive).

<sup>67</sup> May 8, 2020 Letter from National Pork Producers Council to U.S. Department of Justice, available at: <https://www.justice.gov/opa/press-release/file/1276966/download> (asking the federal government to exempt the industry’s mass killing activities from antitrust laws) (“due to severe capacity restrictions at pork packing plants, NPPC, USDA, and industry analysts understand that the need to euthanize a large number (approximately 700,000 per week) of hogs will be unavoidable”).

<sup>68</sup> See USDA APHIS, Nat’l Ag. Biosecurity Ctr. Consortium, *Carcass Disposal: A Comprehensive Review* (Mar. 2004) [USDA, *Carcass Disposal*]. Indeed, burial is placed last on the hierarchy of controls for depopulation efforts for the prevention of disease transmission and is ranked as the worst option among depopulation methods in terms of its impact on pollution and contamination of soil and vegetation. See J. Scudamore et al., *Following the foot and mouth disease outbreaks of 2001*, 21 Rev. Sci. Tech. Off. Int. Epiz., 775-787 (2002); C.L. Gwyther et al., *The environmental and biosecurity characteristics of livestock carcass disposal methods: A review*, 31 Waste Mgmt. 767 (2011).

pits for farmed animals generate contaminants, like ractopamine, that may leach through the soil into the groundwater.<sup>69</sup> Areas with high water tables and sandy soils are at especially high risk of groundwater contamination, because sudden influx of precipitation can raise the water tables and create an easy path for leachates to travel into groundwater.<sup>70</sup>

### **FDA Must Immediately Suspend And/Or Withdraw Approval of Ractopamine Because it Presents an Imminent Hazard and is Unsafe.**

FDA is the primary agency tasked with regulatory oversight of animal drugs. The FDCA's precautionary approach requires FDA to protect humans and animals from substances that *may* be harmful to health.<sup>71</sup> Under FDCA, FDA has authority to immediately suspend approval for any drug that presents an imminent hazard to the health of humans or animals. Additionally, FDA has a duty to withdraw approval for drugs that are shown to be unsafe.

Under the FDCA, FDA may suspend approval of an animal drug immediately if it finds that a drug presents an "imminent hazard to the health of man or animals."<sup>72</sup> An imminent hazard is present:

when the evidence is sufficient to show that a product or practice, posing a significant threat of danger to health, creates a public health situation 1) that should be corrected immediately to prevent injury and 2) that should not be permitted to continue while a hearing or other formal proceeding is being held.<sup>73</sup>

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<sup>69</sup> Pratt & Fonstad, *Geochemical modelling of livestock mortality leachate transport through the subsurface*, 162 *Biosystems Engineering* 67 (2017). Once burial pits are covered, they create anaerobic conditions that limit microorganism breakdown activity. The dead bodies thus cannot decay, creating leachate (*i.e.*, liquids) that enter the surrounding soil and groundwater. See USDA, *Carcass Disposal*, *supra* n.68 at 43. Leachate pollutants from farmed animal carcasses include, *inter alia*, nitrate, ammonia, chloride, and agents found in animal waste. See H.H. Hatzell, *Effects of waste-disposal practices on ground-water quality at five poultry (broiler) farms in north-central Florida, 1992-93*, U.S. Dep't of Interior, US Geological Survey (1995).

<sup>70</sup> Freedman & Fleming, *Water Quality Impacts of Burying Livestock Mortalities*, Presented to the Livestock Mortality Recycling Project Steering Committee, Ridgetown, Ontario (Aug. 2003), available at: [https://www.ridgetownc.com/research/documents/fleming\\_carcassburial.pdf](https://www.ridgetownc.com/research/documents/fleming_carcassburial.pdf) ("Localized contamination may persist for a decade or more in wet soil with a high seasonal water table and low groundwater flow velocity. Even in lightly loaded burial trenches constructed in well-drained soil, complete decay may take two years or more.").

<sup>71</sup> See, *e.g.*, 21 U.S.C. § 342.

<sup>72</sup> 21 U.S.C. § 360b(e)(1)(F).

<sup>73</sup> Proposed Rulemaking, Proposed Statement of Interpretation and Policy regarding Imminent Hazard to the Public Health, 35 Fed. Reg. 18679 (Dec. 9, 1970).

FDA may act to stop an imminent hazard when the injury is expected, even if has not yet occurred.<sup>74</sup> In deciding whether a situation presents an imminent hazard that requires action, FDA must consider the number, nature, severity, and duration of the anticipated injury.<sup>75</sup>

FDA also has a mandatory duty to withdraw approval of an animal drug when it finds the drug to be unsafe,<sup>76</sup> *i.e.*, when use of the drug under approved conditions is not shown to be safe or there is a reasonable basis from which serious questions about the safety of the new animal drug may be inferred.<sup>77</sup> The FDCA provides that FDA *must* withdraw approval for an animal drug if:

- A) “[E]xperience or scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved or the condition of use authorized under [the FDCA];”<sup>78</sup>
- B) New evidence, tests, or methods developed since approval of the application show that the drug is not safe for use “under the conditions of use upon the basis of which the application was approved . . . ;”<sup>79</sup> or
- C) New information, combined with the evidence available at the time the application was approved show a “lack of substantial evidence that such drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof.”<sup>80</sup>

FDA’s inquiry to determine whether to withdraw approval of an animal drug is two-fold. First, FDA determines whether there is a reasonable basis from which “serious questions” about the safety of the new animal drug may be inferred from new scientific evidence. “Serious questions” about the safety of a new animal drug can be raised where the evidence is not conclusive, but merely suggestive of an adverse effect.<sup>81</sup> Second, it determines whether, in light of the new data, the use of the new animal drug under the approved conditions is still considered to be safe.<sup>82</sup>

Because of the ongoing disruption and reduction in slaughterhouse capacity during the COVID-19 pandemic, the continued use of ractopamine presents an imminent hazard to humans, the target animals, and the environment, and is no longer safe. As explained above, animals are

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<sup>74</sup> *Id.*

<sup>75</sup> *Id.*

<sup>76</sup> See 21 U.S.C. § 360b(e); *Rhone-Poulenc, Inc. v. FDA*, 636 F.2d 750, 752-53 (D.C. Cir. 1980) (upholding FDA’s order withdrawing the new animal drug approval for the use of diethylstilbestrol). The term “safe,” as used in 21 U.S.C. § 360b, “has reference to the health of man or animal.” 21 U.S.C. § 321(u).

<sup>77</sup> Ctr. for Veterinary Medicine, FDA, Proposal to Withdraw Approval of the New Animal Drug Application for Enrofloxacin for Poultry, Docket No. 00N-1571, at 2 (Mar. 16, 2004) (Initial Decision).

<sup>78</sup> 21 U.S.C. § 360b(e)(1)(A).

<sup>79</sup> *Id.* at (e)(1)(B).

<sup>80</sup> *Id.* at (e)(1)(C).

<sup>81</sup> *Id.*

<sup>82</sup> Ctr. for Veterinary Medicine, FDA, *Proposal to Withdraw Enrofloxacin*, *supra* n.77.

now forced to remain at CAFOs past the point at which they are normally slaughtered, thereby increasing the duration and cumulative amount of ractopamine they are fed, which in turn increases the risk to their and their handlers' safety and to consumer health. Cows and pigs at CAFOs that cannot send them to the slaughterhouses instead kill them at the CAFO en masse and dispose of them on-site, which increases the risk of environmental contamination.<sup>83</sup> Moreover, real-world use of ractopamine since the time it was approved make clear that it is not safe even under regular conditions. Its use is patently unsafe now that conditions have changed due to COVID-19.

The new reality of the meat supply chain makes FDA's continued approval of the animal drug ractopamine arbitrary and capricious, an abuse of discretion, and not in accordance with the FDCA. In addition, the dozens of studies, reports, and other information concerning the animal health and welfare, human health, and the environment demonstrate that ractopamine is not safe for use as an animal drug. Animal Legal Defense Fund, Food Animal Concerns Trust, and the Center for Biological Diversity therefore urge FDA to immediately suspend or withdraw approval of ractopamine.

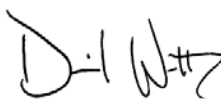
### **C. Environmental Impact Statement**

Pursuant to 21 C.F.R. § 10.30, Petitioners identify that this request for rulemaking is categorically excluded under 21 C.F.R. § 25.33(g).

### **D. Certification**

The undersigned certify that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioners that are unfavorable to the Petition.

Respectfully Submitted,



Daniel Waltz



Cristina Stella

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<sup>83</sup> See *supra* nn.65-70 and accompanying text; see also Elizabeth Royte, *When meat plants shutter, what happens to market-ready animals? U.S. farmers may resort to composting millions of pigs*, Food & Env't Reporting Network, Apr. 28, 2020, available at: <https://thefern.org/2020/04/when-meat-plants-shutter-what-happens-to-market-ready-animals/>. Chuck Abbott, *As Meat Plants Slow, U.S. Will Help Growers Kill Livestock*, Successful Farming, Apr. 27, 2020, available at: <https://www.agriculture.com/news/livestock/as-meat-plants-slow-us-will-help-growers-kill-livestock> (explaining that "because hogs typically reach slaughter weight of around 250 pounds in five or six months from birth and cannot easily be held from market," the president of the National Pork Producers Council said, "Sadly, it is true that euthanization is a question that is coming up on farms"). Indeed, the federal government is considering giving guidance to producers for mass killings. *Id.*

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