PAIGE M. TOMASELLI (State Bar No. 237737)
The Law Office of Paige Tomaselli
P.O. Box 71022
Richmond, CA 94807
T: (619) 339-3180
paige@tomasellilaw.com

CRISTINA R. STELLA (State Bar No. 305475)
Animal Legal Defense Fund
525 E. Cotati Avenue
Cotati, CA 94931
T: (707) 795-2533 ext. 1055
cstella@aldf.org

Counsel for Plaintiffs

THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF CALIFORNIA

ANIMAL LEGAL DEFENSE FUND, FOOD & WATER WATCH, and FOOD ANIMAL CONCERNS TRUST,

Plaintiffs,

v.

ALEX AZAR, Secretary of the United States Department of Health and Human Services; STEPHEN HAHN, Commissioner of the United States Food and Drug Administration; and UNITED STATES FOOD AND DRUG ADMINISTRATION,

Defendants.

Case No.

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

INTRODUCTION

1. Plaintiffs Animal Legal Defense Fund ("ALDF"), Food & Water Watch ("FWW"), and Food Animal Concerns Trust ("FACT") challenge the United States Food and Drug Administration's ("FDA" or "the Agency") approval of and subsequent denial of a petition to stay approval of Experior™ (lubabegron Type A medicated article), a beta 3-adrenergic agonist/antagonist ("β3-AA") manufactured by Elanco US, Inc., that allegedly results in less ammonia gas released from the waste produced by cows raised for beef.

2. FDA approved Experior on November 6, 2018, in violation of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301-399, and the National Environmental Policy Act ("NEPA"), 42 U.S.C. §§ 4321-70. This approval will allow producers to administer this controversial new drug to the nearly 100 million cows raised for beef in the United States despite the facts that FDA did not properly announce the approval in the Federal Register, Experior has not been shown to be safe and effective, and FDA did not adequately consider the drug's environmental impacts.

3. Beta-adrenergic agonist/antagonist ("β-AA") drugs like Experior are linked to significantly higher mortality rates in cows due to a host of fatal respiratory, cardiac, and digestive issues, in addition to significant behavioral issues that make animals more likely to be abused and suffer in ways that directly impact food safety and worker health. These drugs also contaminate the environment.

4. Though the negative effects of beta-agonist drugs are widely known and well established, the beta-agonist subtype to which Experior belongs is the least-studied of all beta-agonist drugs; the specific mechanism of the drug is not yet understood, even by the drug's sponsor.

5. The documents submitted by the drug sponsor as part of its application for approval of Experior illustrate the likelihood it will cause the negative effects typically associated with beta-agonists, and also raise significant uncertainty about additional effects both intended and unintended.

6. The FDCA requires FDA to refuse any new animal drug application where the application does not show that a drug is safe for use, where FDA has "insufficient information" to determine whether a drug is safe for use, or where there is a lack of substantial evidence that the drug will have the effect it purports. FDA must deny—not approve—applications for approval of new animal drugs that cannot be supported by available science.

7. At best, the documents provided to FDA by the drug sponsor in support of its approval are insufficient to establish the drug's safety—at worst, they show it is unsafe. These documents also fail to show that, when actually used under approved conditions, the drug will have its intended effect of reducing the release of ammonia gas.

8. In approving this drug FDA also failed to consider the increased food safety and public health risk of its decision. *β*-AA drug residues end up in meat products and have been linked to human heart and respiratory issues in consumers, producers, and farm workers. *β*-AA drugs also increase the likelihood that an animal will experience injury and stress at industrial animal feeding operations—commonly known as factory farms—and at the slaughterhouse; stress depresses the immune system, making animals more susceptible to pathogens, and increases animals' susceptibility to and shedding of zoonotic bacteria such as *salmonella*. These effects could have wide ranging implications and expose the public to increased health risks.

9. The Environmental Assessment ("EA") prepared in support of Experior's approval also failed to adequately analyze whether the approval will have a significant impact on the environment. The EA made no meaningful attempt to address the cumulative impacts of the current rampant use of *β*-AAs and other animal drugs in cows slaughtered for food in the United States. FDA issued a Finding of No Significant Impact ("FONSI") that did not consider any alternatives, involve the public in the review process, or explain why an Environmental Impact Statement ("EIS") was not required under NEPA. Indeed, FDA's FONSI admits that "both the terrestrial and aquatic environments may ultimately be affected by" Experior; yet, it failed to prepare an EIS addressing this and other potential impacts on an uncounted number of humans, hundreds of thousands of animals, and millions of acres of habitat from the multiple pathways through which Experior is discharged into the environment.

10. On December 6, 2018, Plaintiff ALDF submitted a Petition for Stay of Action ("Petition") to FDA concerning its approval of Experior. ALDF's petition outlined the deficiencies in FDA's approval and illustrated several things: that the approval will cause irreparable harm to Plaintiffs by allowing the use of a drug with known and unknown risks to target animal safety, human health, and the environment and is not consistent with the public interest; that target animal safety and effectiveness and compliance with environmental laws are sound public policy grounds that support a stay; and that public health and other public interests clearly outweigh any delay that would occur while FDA conducts the adequate animal and human health safety tests and environmental review the law requires.

11. FDA denied the Petition on May 20, 2019, based on the same inadequate documents it used to support its underlying decision to approve the drug. Both the decision not to stay the approval and the approval itself violate federal law.

12. On May 21, 2019, one day after denying ALDF's Petition, FDA approved additional drugs that combine the original Experior formulation with controversial antibiotics tylosin and monensin. These combination drug approvals are tiered to, and therefore suffer from the same deficiencies as, the original Experior approval.

13. The FDCA simply does not allow FDA to approve animal drugs without sufficient data to support the drug's safety or efficacy. NEPA similarly requires FDA to thoroughly consider a drug's effects on the environment before approval. These laws mandate that FDA thoroughly assess new drugs and their impacts *before* they are approved; they do not allow FDA and drug manufacturers to subject animals, humans, and the environment to significant harm while they continue to learn about a new drug. And the FDCA's public notice requirement is meant to these regulatory requirements effect.

14. By failing to meet the standards required of it by either statute when it approved Experior and its progeny, FDA violated the FDCA, NEPA, the Administrative Procedure Act ("APA"), and its own regulations. This Court should vacate FDA's unlawful approval of Experior and remand this matter to FDA with instructions to carry out any approval in accordance with federal law.

JURISDICTION AND VENUE

15. This Court has jurisdiction over this action under 28 U.S.C. § 1331 (federal question).

16. Venue is proper in this Court under 28 U.S.C. § 1391(e) because Plaintiff Animal Legal Defense Fund resides in the Northern District of California.

17. Plaintiff Animal Legal Defense Fund resides in the county of Sonoma. Accordingly, assignment to the San Francisco Division or the Oakland Division is proper pursuant to Civil Local Rules 3-2(c) and (d).

18. This Court may award all necessary injunctive relief pursuant to the APA, 5 U.S.C. § 706(1), and may award declaratory relief pursuant to the Declaratory Judgment Act, 28 U.S.C. §§ 2201-02.

PARTIES

19. Plaintiff **Animal Legal Defense Fund** ("ALDF") is a national nonprofit membership organization founded in 1979 in Cotati, California. ALDF's mission is to protect the lives and advance the interests of animals through the legal system. Advocating for effective oversight and regulation of the development, expansion, and pollution of the animal agriculture industry across the United States is one of ALDF's central goals, which it achieves by filing lawsuits, administrative comments, and rulemaking petitions to increase legal protections for animals; by supporting strong animal protection legislation; and by fighting against legislation, like state "Ag Gag" laws, that are harmful to animals and communities surrounding concentrated animal feeding operations ("CAFOs"). Through these efforts, ALDF seeks to ensure transparency in the CAFO system, which is paramount to its ability to protect farmed animals and ALDF members from CAFOs' immensely harmful effects. ALDF has more than 235,000 members and supporters throughout the United States, many of whom live near, recreate near, and closely monitor CAFOs in their communities.

20. Plaintiff **Food & Water Watch** ("FWW") is a national, nonprofit membership organization that mobilizes regular people to build political power to move bold and uncompromised solutions to the most pressing food, water, and climate problems of our

time. FWW uses grassroots organizing, media outreach, public education, research, policy analysis, and litigation to protect people's health, communities, and democracy from the growing destructive power of the most powerful economic interests. Combating the harms associated with industrial farm animal production, also known as factory farming, is one of FWW's priority issues. FWW is engaged in several campaigns to reduce these industrial facilities' pollution, public health threats, harms to rural communities, and animal welfare abuses through stronger regulation and enforcement, increased transparency, and public education and engagement. FWW has more than a decade of experience advocating for stronger FDA oversight of food safety and of products that could harm the environment, including urging stronger oversight of antibiotics used in factory farms and challenging FDA's approval of genetically engineered salmon for human consumption. FWW communicates extensively with our members and supporters, as well as the general public, about FDA's oversight of factory farm practices and other food safety issues, including by releasing reports and fact sheets, issuing press releases and statements, publishing online news pieces, and sending emails and action alerts. FWW has more than one million members and supporters nationwide, and maintains offices across the country, including an office in Oakland, California.

21. Plaintiff **Food Animal Concerns Trust** ("FACT") is a national nonprofit advocacy organization based in Illinois. FACT was founded in 1982 as the first U.S. organization devoted exclusively to addressing the public health problems that result from raising farm animals in confined and inhumane conditions. FACT promotes the safe and humane production of meat, milk, and eggs, and envisions and advocates for a food system in which all food-producing animals are raised in a healthy and humane manner so that everyone will have access to safe and humanely-produced food. With a particular focus on eliminating or curbing the use of antibiotics and drugs given to food-producing animals in order to protect consumers from drug residues, FACT has long been concerned about both the human health impacts from the use of beta-agonist drugs and their impact on animal health and welfare. FACT advocates for responsible use of animal drugs by surveying producers and publishing reports and "score cards" to educate the public and regulators on the use of animal drugs in the food system. FACT also

advocates directly to FDA for the withdrawal of beta-agonists. In 2013, FACT successfully petitioned and sued FDA to remove arsenic-containing drugs from the food supply.

22. Plaintiffs and their members and supporters have a strong interest in preventing FDA approval of unsafe animal drugs that may harm public health, the environment, or animal health and welfare. They and their members and supporters are particularly concerned that FDA's approval of Experior will further entrench the harmful factory farm system by making it possible for large feedlots to "greenwash" their operations by claiming lower emissions of ammonia, which is known to harm human health, rural quality of life, and the environment; they are harmed by FDA's decision to approve an animal drug that is likely to increase cow herd size and density at feedlots, and that could encourage construction of new feedlots. ALDF and FWW members and supporters, and the consumers on whose behalf FACT advocates, also eat beef from cows raised on feedlots and are concerned that FDA's approval of a novel drug could affect the safety of the meat they eat through drug residues and through the increased risk of contamination and foodborne illness from animals that Experior may render nonambulatory. ALDF and FWW also have members and supporters who live and recreate near, and are adversely impacted by, contaminated air and water and odors from feedlots. They also have aesthetic interests in the health and lawful treatment of farmed animals. These injuries to Plaintiffs and their members and supporters will be redressed if Plaintiffs prevail in this action.

23. Defendant **Alex Azar** is the Secretary of the United States Department of Health and Human Services, which includes FDA. The Secretary of the U.S. Department of Health and Human Services, "through the Commissioner" of FDA, regulates new animal drugs. 21 U.S.C. § 393(d)(2). Secretary Azar is named a Defendant solely in his official capacity.

24. Defendant **Steven Hahn** is the Commissioner of FDA. In that capacity, he is directly responsible for overseeing the FDA review process for the Experior application and is tasked with the authority to approve, deny, or withdraw approval for Experior upon a finding that applicable legal requirements have or have not been met. Commissioner Hahn is named as a Defendant solely in his official capacity.

25. Defendant **U.S. Food and Drug Administration** is a federal agency within the U.S. Department of Health and Human Services. FDA is charged with the regulation of medical products, tobacco, foods, and veterinary medicine. As described by the agency itself, FDA is responsible for protecting public health by ensuring that human and veterinary drugs are safe and effective.

STATUTORY AND REGULATORY FRAMEWORK

Federal Food, Drug, and Cosmetic Act and FDA Regulations

26. In enacting the FDCA in 1938, Congress provided FDA the authority and obligation to protect public health and safety by overseeing certain food products, drugs, and cosmetics. Through the FDCA, Congress charged FDA with "promot[ing] the public health" by ensuring that "human and veterinary drugs are safe and effective." 21 U.S.C. § 393.

27. A "new animal drug" is any drug intended for use in animals that has not been used to a material extent or for a material time and is not recognized by "experts qualified by scientific training and experience" as safe and effective for use under the conditions prescribed. *Id*. § 321(v).

28. A new animal drug is deemed "unsafe" unless FDA has approved a new animal drug application for the drug and its use conforms to its labeling and the conditions of the approved application. *Id*. § 360b(a)(1).

29. The FDCA requires an applicant to submit reports to demonstrate whether its drug is "safe and effective for use." *Id*. § 360b(b)(1)(A). The applicant must also submit "other use restrictions . . . in order to assure that the proposed use of such drug will be safe." *Id*. § 360b(b)(1)(H). FDA regulations require an applicant to submit evidence to establish the "safety and effectiveness" of a new animal drug. 21 C.F.R. § 514.1(8).

30. The FDCA requires FDA to refuse any new animal drug application where: the results of "adequate tests by all methods reasonably applicable" either "show that such drug is unsafe for use under [prescribed] conditions or do not show that such drug is safe for use under such conditions"; it "has insufficient information to determine whether such drug is safe for use under such conditions"; or "there is a lack of substantial evidence that the drug will have the

effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof." 21 U.S.C. § 360b(d)(1).

31. The FDCA does not define the phrases "safe and effective" or "safety and effectiveness," or the term "effective." The statute states generally that the term "safe" "has reference to the health of man or animal." *Id.* § 321(u). But in considering whether a drug is "safe," FDA may consider, among other things: (1) "the cumulative effect on man or animal of such drug"; (2) "safety factors" that experts consider appropriate; and (3) whether the conditions in the proposed labeling are reasonably certain to be followed. *Id.* § 360b(d)(2). When evaluating the sufficiency of the information about a drug's safety and effectiveness, FDA must similarly consider "(A) the probable consumption of such drug and of any substance formed in or on food because of the use of such drug, (B) the cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, (C) safety factors which in the opinion of experts, qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data, and (D) whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice." 21 C.F.R. § 514.111(a)(4).

32. The FDCA requires FDA to publish approval of new animal drug applications in the Federal Register. 21 U.S.C. § 360(i). This notice must include "conditions and indications of use of the new animal drug . . . and such other information, . . . as the Secretary deems necessary to assure the safe and effective use of such drug." *Id.*; *see also* 21 C.F.R. § 514.105.

33. FDA's authority to oversee and enforce approvals of new animal drugs is tied to the continued "safety" of a drug. A drug is considered "unsafe" post-approval if its use does not conform to the approved application. 21 U.S.C. § 360b(a)(1)(A). FDA also has authority to withdraw approval of a new animal drug if it finds that its use is "unsafe" even under the approved conditions or if the applicant makes any changes from the standpoint of "safety or effectiveness." *Id.* § 360b(e)(1).

34. An interested person can, within 30 days of the approval, request that FDA stay a particular approval pending further review. 21 C.F.R. § 10.35(b). FDA's Commissioner must

grant a stay in any proceeding if all of the following apply: (1) the petitioner will otherwise suffer irreparable injury; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting a stay; and (4) the delay resulting from the stay is not outweighed by public health or other public interests. *Id.* at (e)(1).

National Environmental Policy Act

35. NEPA is "our basic national charter for protection of the environment." 40 C.F.R. § 1500.1(a). NEPA emphasizes the importance of comprehensive environmental analysis and requires the action agency—here, FDA—to make informed decisions by taking a "hard look" at potential environmental consequences before taking action. It also ensures that "environmental information is available to public officials and citizens before decisions are made and before actions are taken." *Id.* § 1500.1(b).

36. All "major Federal actions significantly affecting the quality of the human environment" require the preparation of a detailed EIS by the action agency. 42 U.S.C. § 4332(2)(C). Thus, a threshold determination is whether a proposed project may "significantly affect" the environment.

37. Congress created the Council on Environmental Quality ("CEQ") to implement NEPA by promulgating regulations applicable to all federal agencies. *Id.* § 4342.

38. CEQ's regulations direct agencies to prepare an EA to determine whether the proposed action will have a significant impact on the environment and warrant the preparation of an EIS. 40 C.F.R. § 1508.9. An EA must provide sufficient evidence and analysis to allow an agency to determine whether it should prepare an EIS or a FONSI.

39. CEQ regulations require an agency to consider the direct, indirect, and cumulative impacts of a proposed action's impact on the environment, as well as "considerations of both context and intensity." *Id.* §§ 1508.8, 1508.27. Context considerations include analysis of the action's impact on affected regions, varying by the locality of the action, as well as national and societal impacts. *Id.* § 1508.27. Intensity refers to the severity of the impact, and requires the

agency to consider ten factors, including, among others: beneficial and adverse impacts; public health or safety impacts; unique characteristics of the affected geographic area, such as proximity to ecologically critical areas; the degree to which the effects are likely to be highly controversial; highly uncertain risks; precedential effects; cumulatively significant impacts; and adverse effects on threatened and endangered species. *Id.*

40. NEPA further requires agencies to "rigorously explore and objectively evaluate all reasonable alternatives." *Id.* § 1502.14(a); 42 U.S.C. § 4332(2)(E).

41. If an agency decides not to prepare an EIS, it must explain why a project will not have a significant effect on the environment. 40 C.F.R. § 1508.13.

42. A new animal drug application must either contain an EA or present an analysis and justification for why the applicant believes that it qualifies for a categorical exclusion under NEPA. 21 C.F.R. § 514.1(b)(14). Consideration of this information is integral to FDA's review of the application. *See id.* § 514.110(b)(10). FDA must reject the application if "[t]he applicant fails to submit an adequate environmental assessment . . . or fails to provide sufficient information to establish that the requested action is subject to categorical exclusion . . . ." *Id.* § 514.111(a)(9).

43. FDA's regulations categorically exclude new animal drug applications and supplemental New Animal Drug Applications from NEPA review *only if* the action does not increase the use of the drug. *Id.* § 25.33(a).

44. A normally categorically excluded action requires at least an EA if "extraordinary circumstances" indicate that the proposed action "may significantly affect the quality of the human environment." *Id.* § 25.21. FDA's regulations cite the CEQ context and intensity regulations for examples of significant impacts and explicitly provide two examples of extraordinary circumstances: actions where "there is potential for serious harm to the environment," and actions that adversely affect listed threatened or endangered species or their critical habitat. *Id.*

//

//

Administrative Procedure Act

45. The APA grants a right of judicial review to "[a] person suffering legal wrong because of agency action, or adversely affected or aggrieved by agency action . . . ." 5 U.S.C. § 702.

46. Under the APA, a court must "hold unlawful and set aside agency action . . . found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law . . . ." *Id.* § 706(2)(A). An agency action is "arbitrary and capricious if the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Assoc. v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

47. Under the APA, a court must also "hold unlawful and set aside" any agency action taken that is "in excess of statutory jurisdiction, authority, or limitations, or short of statutory right." 5 U.S.C. § 706(2)(C).

48. Finally, under the APA, a court shall also "hold unlawful and set aside" any agency action that was promulgated "without observance of procedure required by law." *Id.* § 706(2)(D).

FACTS

Beta-Agonists

49. Experior is part of the beta-adrenergic agonist/antagonist ("beta-agonist" or "*β*-AA") family. The *β*-AA family was first described more than 60 years ago and has been divided into three subtypes: *β1*, *β2*, and *β3*. Experior belongs to the beta 3-phenethanolamine adrenergic agonist/antagonist ("*β*3-AA") subtype.

50. Beta-agonists are widely used in meat production in the United States due to their efficacy in increasing animal growth. For pigs alone, around 60-80% of those raised for food in the United States receive beta-agonists, amounting to tens of millions of animals each year.

51. 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 overall carcass weight, increasing the profit margin for producers.

52. Available research, including from FDA's own files[1], shows that beta-agonists have substantial negative impacts on animal health, human health, and the environment.

53. Because beta-receptors are spread widely throughout the body as part of the sympathetic nervous system, a number of physiological side effects can manifest when these drugs are administered to animals.

54. 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 that makes it harder for the heart to pump blood to the rest of the body, and other "adverse effects" on the heart. 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.

55. 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 fatigued cattle syndrome. These conditions make animals more difficult to handle, increasing the incidence of violence towards animals by handlers at feedlots and slaughterhouses, while also increasing the potential for handlers to be injured.

56. Because Experior negatively influences animal behavior, it corresponds to an increased risk to humans who work with them. The beta-agonist Zilpaterol, for example, was voluntarily withdrawn by its drug sponsor, Merck, because slaughterhouses throughout the

[1] From 2013 to 2019 Plaintiff ALDF received voluminous FDA records related to beta-agonists as the result of litigation under the Freedom of Information Act. FDA had these records in its possession at the time it approved Experior.

United States reported concerns about non-ambulatory, slow, and difficult-to-move cows, and cows with severely deteriorated hooves.

57. FDA's own files contain reports of adverse reactions to beta-agonists in workers and producers in the animal agriculture industry, as well as reports of beta-agonist residues in meat harming consumers. FDA has received numerous complaints from workers and consumers who experienced nausea, dizziness, respiratory issues, and other serious medical conditions requiring treatment and hospitalization, all after either being directly exposed to or consuming meat from animals fed beta-agonists.

58. FDA's files also contain acknowledgements from its own scientists that humans with compromised cardiovascular systems react adversely to beta-agonists, and in fact FDA scientists encouraged beta-agonist drug sponsors to investigate cardiac issues in further beta-agonist studies after tremors were seen in a pilot study. FDA scientists have also stated that beta-agonists' "[e]ffects are not desirable for consumers of food containing residues of the drug."

59. 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, a popular beta-agonist, in pig production. The European Food Safety Authority panel that banned the drug based its decision in part on the fact that its data could not support a conclusion that the drug is safe.

60. Beta-agonists also harm the environment. Animals excrete approximately 95% of the beta-agonist ractopamine that they ingest in the first three days after consumption, 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 on the feedlot, further leaching the drugs into the environment. These discharges degrade water quality both for recreation and drinking water. This is significant with respect to Experior, specifically: with a half-life of 723 days, it persists in the environment long after it is excreted. FDA's approval of Experior will add substantially to the cumulative amount of beta-agonists in the environment, thereby compounding their cumulative environmental effects.

61. Finally, because the use of β-AAs 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 raised or finished in feedlots already suffer from stress due to their living conditions or 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.

Beta-Agonist Combinations: Monensin & Tylosin

62. Monensin is a polyether carboxylic ionophore antibiotic widely used in ruminant animal feed, including cows raised for food.

63. FDA approved monensin in 1970. *See* NADA 38-878, 35 Fed. Reg. 7734 (May 20, 1970).

64. Monensin is used for the treatment of coccidiosis in several animals, including cows raised for food. Monensin is also used to control ketosis and bloat and is used as a growth promoter. Monensin can be used as a growth promoter feed additive in cows raised for food because it is not used in human medicine and was therefore not classified as a critically important antibiotic for humans by the World Health Organization ("WHO").

65. Researchers have shown that cows fed monensin excrete more than 50% of the drug into the environment through feces. Studies have frequently detected this excreted monensin in CAFO wastewater and groundwater near CAFOs and feedlots.

66. In 2006, the European Food Safety Authority explained that under typical dosages and conditions, monensin poses a risk to soil organisms. Even in low doses monensin has toxic effects on soil organisms.

67. Non-target animals are at a significant risk—including risk of death—from exposure to small doses of monensin.

68. Tylosin is an antibiotic and a bacteriostatic feed additive used in veterinary medicine to treat liver abscesses in cows raised for food.

69. FDA first approved tylosin for use as a veterinary drug in 1961. *See* NADA 012-491, 26 Fed. Reg. 4369 (May 19, 1961).

70. Tylosin is also used in human medicine. WHO and FDA consider tylosin "critically important" to human medicine.

71. Tylosin was used historically as a growth promoter, but FDA now only allows its use for "disease prevention." The line between growth promotion and disease prevention is blurred: producers can still use tylosin on a daily basis to prevent liver abscesses in cows raised for food. Up to a third of cows on feedlots—where cows raised for food are fattened for up to six months before slaughter—suffer from liver abscesses.

72. Studies have shown that when tylosin is used at CAFOs, it leads to the development of tylosin-resistant bacteria. Using tylosin fuels resistance to erythromycin, an antibiotic used to treat people with chest infections, ear infections, and sexually transmitted diseases.

73. The European Union banned the use of tylosin as a growth promotor in 1999, with additional restrictions preventing its long-term use, because of its potential to render its use as a human antibiotic ineffective.

74. Under FDA rules, tylosin can still be administered on a daily basis for months at a time.

75. Tylosin was approved before Congress enacted NEPA. Upon information and belief, FDA has not addressed the environmental impacts of tylosin when fed to cows in a publicly available NEPA document.

76. Tylosin is commonly found in surface water. For example, a 2002 survey of surface waters in the United States found tylosin in 13.5% of streams sampled. Tylosin's surface water half-life is approximately 200 days. In 2006, Applied and Environmental Microbiology concluded that "high levels of tylosin resistance persisted for years after usage" in soil. In 2004,

the Journal of Occupational and Environmental Hygiene found tylosin-resistant bacteria in the soil and air near CAFOs.

Beef Production in the United States

77. Cows are raised for beef in all 50 states. There are 913,246 cow and calf operations in the United States that raise 94.8 million cows each year, 31.8 million of whom are raised exclusively for beef.[2]

78. While the natural diet for cows is made up of forage (pasture, silage, hay), many cows are "finished" in feedlots on grain as a cost-effective way to increase animal weight, to save time, and reduce total feed. Though the natural lifespan of a cow is 20 years, cows raised for beef are slaughtered at the age of 2 or 3.

79. Feedlots are a type of CAFO, which are characterized by high concentrations of animals who are confined in a manner that maximizes efficiency at the expense of animal health and well-being. These operations, which have become pervasive throughout the United States, harm water quality and quantity, endangered species, the confined animals themselves, community health, and other aspects of the human environment.

80. These harms outweigh any alleged benefit of increased production; CAFOs are simply not a viable or sustainable way to raise animals used as food.

81. Scientific research and government agency studies confirm the varied and disastrous impacts of CAFOs.

82. CAFOs are one of the largest sources of water pollution in the country.

83. The U.S. Environmental Protection Agency ("EPA") has found that "[a]gricultural operations, including CAFOs, now account for a significant share of the remaining water pollution problems in the United States."[3] Indeed, agriculture "is the leading

[2] National Cattleman's Beef Association, Industry Statistics, https://www.ncba.org/beefindustrystatistics.aspx (last visited May 19, 2020).

[3] National Pollutant Discharge Elimination System Permit Regulation and Effluent Limitation Guidelines and Standards for Concentrated Animal Feeding Operations (CAFOs), 68 Fed. Reg. 7176, 7181 (Feb. 12, 2003).

contributor of pollutants to identified water quality impairments in the Nation's rivers and streams."[4] Twenty-nine states have recently made similar findings, identifying animal feeding operations as contributors to water quality impairment in EPA's 2009 National Water Quality Inventory. 76 Fed. Reg. 65431, 65434 (Oct. 21, 2011).

84. Confined animals used for food in the United States produce roughly 500 million tons of manure per year, more than sixty-five times the mass of human biosolids treated by publicly owned treatment works. A single cow raised for beef is estimated to produce about 100 times the waste of a single human; a feedlot raising just 1000 cows for beef thus produces as much waste as a city of 100,000 humans.

85. Unlike concentrated human waste, which is handled by wastewater treatment plants that decompose and disinfect the waste to reduce its threat to water quality, CAFOs generally transfer animal waste into huge pits or basins, where they hold the manure until spreading it onto fields without much, if any, prior treatment.

86. The drugs excreted in animal waste are not treated or removed before the manure enters the environment.

87. CAFOs operate, and thus produce waste, throughout the year. Because crops do not grow throughout the year in many regions where CAFOs are prevalent, and waste applied to the ground when crops are not growing increases the risk of runoff, CAFOs must store waste for long periods of time and sometimes apply waste to fields even when the risk of runoff is high. Unlined or inadequately lined manure storage lagoons can contaminate communities' well water if the manure leaks through the soil into aquifers below.

88. When manure from these massive stockpiles is eventually applied to the ground or crops, it is usually sprayed or otherwise disposed of onto land without barriers between fields and waterways. Runoff, drainage, or percolation from land application of manure can contaminate surface waters with the pharmaceuticals administered to the animals, threatening the health of the aquatic ecosystem and members of the public who swim or recreate in the

[4] *Id.*

waterways. CAFOs can also affect groundwater quality by increasing salinity and contributing contaminants including pharmaceuticals. Thus, the CAFO system of manure disposal contaminates surface and ground waters used for drinking and recreation, and by imperiled species.

89. Nitrate contamination from cow manure can also cause downstream communities to bear significant costs to treat municipal drinking water. *See Bd. of Water Works Trustees of City of Des Moines, Iowa v. Sac County Bd. of Supervisors*, 890 N.W.2d 50, 54 (Iowa 2017) (stating that the Des Moines Water Works spends approximately $4,000-$7,000 per day to treat water contaminated by agricultural nitrate pollution, and that the Water Works will need to invest $260 million to design and construct a larger treatment facility to ensure that water remains safe for human consumption).

90. Further, when manure pollutes surface water during winter and spring months, the contamination contributes to the creation and expansion of toxic blue-green algae blooms during the summer, which also impact public water supplies. For example, in 2014, a blue-green algae bloom caused the City of Toledo, Ohio to order its residents not to use public water for drinking, cooking or bathing.[5] Surface water pollution from CAFO waste has also led to algae blooms linked to major fish die-offs, significant decline of underwater plants, and odors and bacterial contamination that deter people from recreating on rivers, lakes, and other watercourses. Contaminated groundwater can also move laterally and enter rivers and streams to contaminate those surface waters.

91. The concentration of animals at CAFOs also produces air pollutants, including ammonia that Experior purports to reduce. However, reducing ammonia emissions while confining the same or greater numbers of cows in CAFOs will do nothing to alleviate the overall air impacts of CAFOs because CAFOs emit a variety of air pollutants, including hydrogen sulfide, methane, nitrous oxide, volatile organic compounds, and particulate matter. They also

[5] Carolyn L. McCarthy et al., Community Needs Assessment After Microcystin Toxin Contamination of a Municipal Water Supply – Lucas County, Ohio, September 2014, 65 Morbidity & Mortality Weekly Report 925 (2016), https://www.cdc.gov/mmwr/volumes/65/wr/mm6535a1.htm.

emit pathogens—including those that carry antimicrobial resistance—and particles of bedding, manure, and other allergens. The number of animals at a CAFO is generally proportional to the air pollution it emits.

92. The U.S. Centers for Disease Control and Prevention consider airborne emissions from CAFOs to "constitute a public health problem." Air emissions can cause serious and life-threatening health problems, and even death. The health problems include respiratory illnesses, irritation to the eyes, nose, and throat, anxiety and depression, memory loss, and heart disease. The effects are amplified in vulnerable populations like children and the elderly.

93. Hydrogen sulfide, for example, is a flammable, poisonous asphyxiant that produces an odor similar to rotten eggs. Hydrogen sulfide can cause difficulty breathing, loss of consciousness, shock, pulmonary edema, coma, brain damage, and death. Survivors of hydrogen sulfide poisoning commonly have neuropsychiatric defects, some of which can be permanent. Exposure to higher levels of hydrogen sulfide is immediately hazardous to human life and health. It can cause rapid loss of consciousness, then death, after one or two breaths. This has been referred to as the "slaughterhouse sledgehammer" effect. Even at low concentrations, hydrogen sulfide causes strong odors in areas surrounding CAFOs. The National Research Council has found hydrogen sulfide emissions from CAFOs to have a "significant" effect on the quality of human life.[6]

94. CAFOs and CAFO waste disposal also release the powerful greenhouse gases methane and nitrous oxide. Methane and nitrous oxide—two of the six greenhouse gases that "together constitute the root cause" of climate change and its "resulting impacts on public health and welfare," 74 Fed. Reg. 66517 (Dec. 15, 2009)—are 20 and 300 times more powerful than carbon dioxide at trapping heat in the atmosphere over a 100-year period, respectively. Methane is produced by anaerobic decomposition of organic matter in biological systems and by the normal digestive process in ruminant animals. Nitrous oxide is typically a product of a microbial process occurring in soils and fertilizer via decomposition of livestock manure and urine. In

[6] Nat'l Research Council, *Air Emissions from Animal Feeding Operations: Current Knowledge, Future Needs* (2003).

2006, industrial animal agriculture was responsible for emitting almost nine million tons of methane in the United States alone. Increases in methane emissions correlate with the consolidation of the CAFO industry, with EPA reporting a 34% increase in methane emissions from manure management between 1990 and 2006.[7] Agricultural soil management activities, which include application of manure to the soil—particularly the application of liquid manure, as typically results from CAFOs' use of manure lagoons—are the largest source of nitrous oxide emissions in the United States, producing approximately 72% of nitrous oxide emissions in 2006.

95. CAFOs are also a significant source of volatile organic compound (VOC) emissions. EPA defines VOCs as "any compound of carbon, excluding carbon monoxide, carbon dioxide, carbonic acid, metallic carbides or carbonates, and ammonium carbonate, which participates in atmospheric photochemical reactions." 40 C.F.R. § 51.100(s). CAFOs emit VOCs through feed decomposition, fresh waste, enteric processes, and manure decomposition. CAFOs emit as many as 165 VOCs; of these, 24 are odorous chemicals and 21 are listed as Hazardous Air Pollutants under the Clean Air Act. 42 U.S.C. § 7412(b). CAFO-emitted Hazardous Air Pollutants include benzene, formaldehyde, tetrachloroethylene, methanol, toluene, and xylene. VOCs also react with other pollutants to form ground-level ozone, which causes a range of serious health effects. Some VOCs are toxic to the nervous system in both humans and animals. Studies examining neurobehavioral issues among humans living near CAFOs have found increased rates of depression, anger, fatigue, and confusion.[8] At least one study has shown VOCs can also cause serious problems in animals, including delayed weaning, higher stress levels, and reduced growth and appetite. Other effects include deteriorated muscles, organs, and respiratory functioning, and increased morbidity and mortality.

---

[7] EPA, Report No. EPA-430-R-08-005, *Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990-2006* (2008). That increase has rapidly grown in recent years, to a 65% increase between 1990 and 2014. EPA, Report No. EPA-430-R-16-002, *Inventory of U.S. Greenhouse Gas Emissions and Sinks: 1990-2014*, at 5-9 (2016).

[8] *E.g.*, S. Schiffman et al., *Quantification of Odors and Odorants from Swine Operations in North Carolina*, 1089 Agric. & Forest Meteorology 213 (2001).

96. CAFOs also directly emit particulate matter, including particles of dry manure, bedding and feed materials, biological matter, and dusts. Indeed, CAFOs persistently cause National Ambient Air Quality Standards (NAAQS) exceedances because of their releases of VOCs and particulate matter.

97. Haze from CAFOs drastically reduces visibility, creates significant losses of public enjoyment of wildlife and wilderness areas, and harms tourism-dependent communities.

98. CAFOs routinely provide continuous doses of antibiotics to every animal confined within the facility, regardless of whether the animal is sick. Routine antibiotics are supposed to be primarily used to prevent sickness due to crowded, stressful confinement conditions.

99. Continuous, herd-wide and flock-wide use of antibiotics at CAFOs leads to the development and spread of antibiotic-resistant bacteria; giving antibiotics to an entire group of animals at a facility in steady, low doses "strongly encourages" drug resistance, "especially when provided in feed or water, where they remain active and are widely dispersed."[9] This resistance is then readily transmitted to surrounding bacteria.

100. Antimicrobial-resistant pathogens are capable of transferring to humans, and jump from manure, live animals, and animal carcasses at CAFOs to human populations via various environmental pathways. These pathways include through the air as dust, up from the soil into edible crops, into groundwater and surface waterways, and through the food chain during slaughter processes.

101. Scientific research and government findings tie antibiotic use in the raising of food-producing animals to increased antimicrobial resistance in bacterial populations in animals, the environment, and humans.

102. Indeed, a recent study of veterans in rural Iowa found that the risk of antibiotic-resistant Staphylococcus aureus (a bacteria species) was 88% higher among veterans living

[9] Stuart B. Levy, *Multidrug Resistance—A Sign of the Times*, 338 New Eng. J. of Med. 1376, 1377 (1998); *see also* White House, National Action Plan for Combating Antibiotic-Resistant Bacteria 20 (2015).

within one mile of high-density pig CAFOs.[10]

103. Upon human exposure, the resistant bacteria can colonize the human gut and cause illnesses resistant to clinically important antibiotics.

104. Antibiotic-resistant bacteria are such a significant threat that the United Nations General Assembly, acting for only the fourth time on a public health issue and the first time since the Ebola outbreak in 2014, declared resistance a "most urgent global risk."[11] In 2014, President Obama issued an Executive Order declaring, "Combating antibiotic resistant bacteria is a national security policy." Exec. Order No. 13,676 (Sept. 18, 2014).

105. Along with antibiotic resistance, CAFOs put public health at risk through the spread of foodborne illnesses, which kill approximately 3,000 Americans, hospitalize 128,000, and sicken 48,000,000 every year. Foodborne *E. coli* in beef products are responsible for the most deaths each year. Stressed, injured, and non-ambulatory cows are more likely to contract bacterial infections, exposing workers and consumers to higher levels of dangerous bacteria.

106. Experior also enables CAFO operators to confine more cows per feedlot while touting lower ammonia emissions, thereby exacerbating the existing animal, public, and environmental health effects of the CAFO industry. And because CAFOs are shrouded in government-sanctioned secrecy, exempt from critical environmental reporting, and hidden behind claims of confidential business information, the public is all but helpless to prevent CAFOs' harms while at the same time forced to support their very existence with their tax dollars.

//

//

//

---

[10] *See* M. Carrell 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. Control Epidemiology 190 (2014).

[11] Press Release, United Nations, High-Level Meeting on Antimicrobial Resistance (Sept. 21, 2016), http://www.un.org/pga/71/2016/09/21/press-release-hl-meeting-onantimicrobial-resistance.

FDA's Approval of Experior

107. On November 6, 2018, FDA announced on its website that it had approved Experior for use in cows raised for meat.[12] FDA did not publish the approval in the Federal Register, notwithstanding the Agency's 30-day timeline by which to file a Petition for Stay of Action under 21 C.F.R. § 10.35.

108. Experior's primary approved use is to reduce the ammonia gas released as a by-product of animal waste when fed under specific conditions to cows raised for beef on feedlots.

109. The approval of Experior is the first time FDA has approved a drug that purports to reduce gas emissions from an animal or its waste, increasing the need for thorough animal health and environmental studies about the potential effects of this drug.

110. FDA's November 6, 2018, approval was based on its narrow review of the drug sponsor's application, EA, and supporting documents. FDA's approval touted the potential environmental benefits of Experior—many of which are unsubstantiated in the corresponding approval documents—but cautioned that the studies on which FDA relied "did not measure ammonia gas emissions on a herd or farm scale and could not take into account other factors that may affect ammonia gas emissions, such as wind speed and direction, rainfall, weather, input from other nitrogen sources and manure management. Therefore, extrapolation to the herd, farm or larger scale could not be accurately or reliably predicted."[13]

111. On December 6, 2019, Plaintiff ALDF submitted a timely Petition for Stay of Action under 21 C.F.R. § 10.35, requesting that FDA stay the approval of NADA 141-508 for Experior and the corresponding EA and FONSI.[14]

[12] FDA, FDA Approves Experior for Reduction of Ammonia Gas Released from Beef Cattle Waste (Nov. 6, 2018), https://www.fda.gov/animal-veterinary/cvm-updates/fda-approves-experior-reduction-ammonia-gas-released-beef-cattle-waste.

[13] *Id*.

[14] *See* Animal Legal Defense Fund, Petition for Stay of Approval of Experior (Dec. 6, 2019), https://www.regulations.gov/document?D=FDA-2018-P-4656-0001.

112. ALDF's Petition outlined various deficiencies in FDA's approval. For example, ALDF's Petition illustrated that Experior has not been shown to be safe and effective in target animals, in violation of the FDCA, because Experior may have significant adverse consequences for animal health, including heat stress, lameness, and sudden death; and FDA admits that it could not make reliable predictions about the effectiveness of Experior at a herd, farm, or larger scale. ALDF further illustrated the potential for Experior to cause significant harm to the environment, underscoring FDA's duty to conduct an EIS under NEPA. Finally, ALDF explained that FDA's approval documents failed to consider any alternatives to the approval or to even mention threatened and endangered species, also violating NEPA. ALDF's Petition showed that Experior is unsafe, or at best, that FDA lacked sufficient information to approve the drug. An approval that does not meet the FDCA's and NEPA's requirements causes irreparable harm to Plaintiffs because it legitimizes the use of a drug with known and unknown risks to target animal safety, human health, and the environment. ALDF requested that FDA stay the approval of Experior unless and until these and other deficiencies are corrected, and the agency action is in compliance with the referenced statutes.

113. FDA did not publish notice of the Experior approval in the Federal Register until April 2, 2019, well after the 30-day deadline to petition for a stay of the action.

114. On May 20, 2019, FDA denied ALDF's Petition. FDA erroneously determined that the Petition did not meet the conditions set out in 21 C.F.R. § 10.35(e) requiring issuance of a stay. FDA further found that the Petition did not demonstrate that issuance of a stay under the Commissioner's discretion would be appropriate (i.e., in the public interest and in the interest of justice as set forth in 21 C.F.R. § 10.35).

115. FDA's response to ALDF's Petition was insufficient to justify both FDA's approval and its denial of the Petition. As explained below, the information provided by FDA in the Freedom of Information (FOI) Summary—the publicly-available summary of safety and effectiveness information that supports a new animal drug application—and reiterated by FDA in its response to ALDF did not contain sufficient data to refute or confirm the possible target animal safety impacts posed by Experior, could not confirm the effectiveness of Experior, and

highlighted the myriad unknowns of how Experior will affect cows raised for beef when used under expected conditions.

116. FDA's response also underscored the potential environmental impacts associated with Experior. As explained below, FDA did not—either originally or in response to ALDF's Petition—adequately consider the effects that the presence of Experior in cow feces will have on the environment. FDA did not consider the cumulative environmental effects of the use of the drug over time or in combination with other drugs, and especially other beta-agonists that are already present in the environment. FDA conducted only the most cursory review of the impact Experior may have on invertebrates and aquatic species other than rainbow trout. FDA did not review the potential impacts of Experior on bees and pollinators. FDA thus lacked sufficient information to conclude that Experior would not significantly affect the environment or threatened and endangered species.

117. One day after denying ALDF's Petition, on May 21, 2019, FDA approved two Experior combination drugs, one with tylosin and one with monensin. FDA did not publish notice of these approvals in the Federal Register until October 7, 2019. These drug approvals tiered to FDA's approval of the original Experior formulation without any additional assessment of the cumulative impacts of these additional approvals, despite the fact that the additional approvals will increase the overall use of Experior in the United States.

Specific Deficiencies in FDA's Approval and Stay Denial

Drug Safety in Target Animals

118. The FDCA requires FDA to refuse any new animal drug application that has not been shown to be safe in target animals or where there is insufficient data to establish drug safety. The safety studies referenced in the FOI Summary fail to establish that the drug is safe for target animals.

119. Overall, the studies on which FDA relied contained inadequate experimental conditions to simulate feedlots and were based on small sample sizes. These studies are simply

not able to accurately determine if and to what degree there will be an increase in serious health effects in cows, including fatal conditions that are known to be caused by *β*-AAs.

120. Most of the trials FDA reviewed were designed to measure ammonia and did not look adequately at biologically plausible and probable adverse events, including (but not limited to) lameness and overheating.

121. Where FDA did acknowledge the occurrence of adverse events, it dismissed them without explaining or addressing them.

122. For example, *β*3-AAs including Experior are thermogenic, meaning they increase heat in the body through metabolic stimulation. The resulting increase in body temperature, especially in conjunction with the high environmental temperature that is common on feedlots, may cause or exacerbate serious or deadly adverse reactions in cows. Nevertheless, FDA failed to adequately consider Experior's contribution to heat stress. The studies cited in the FOI Summary failed to measure cortisol levels or other standard stress indicators, and the sample sizes in the trials cited in the FOI Summary are too small to be able to discern whether there might be an increased risk of sudden death from overheating due to the drug. The animals subjected to the studies on Experior were not heat stressed and the studies failed to account for the likelihood of high temperatures on feedlots.

123. FDA's FOI Summary states that "[r]espiratory and digestive issues were the most common abnormal health effects noted." One of the first signs that a cow raised for beef is unhealthy is reduced appetite and growth. Studies indicate that animals fed Experior experienced poor appetite and other gastrointestinal issues (e.g. bloat), which repeatedly led to animals dying. Lameness was also widespread in the studies; animals fed Experior had a numerically higher incidence of lameness compared to the control group. Yet FDA dismissed these findings as non-significant.

124. When studied in humans, scientists found *β*3-AAs in higher levels in human melanomas and other tumors. *β*3-AAs are also known to increase blood pressure in humans. Yet the FOI documents do not address the effects and implications (if any) this may have on cows.

125. FDA further erroneously determined that Experior does not exhibit any *β*2-AA activity. Experior does exhibit some *β*2-AA activity. *β*2-AAs are associated with many adverse events in cows and pigs, such as trembling, lameness, inability to rise or walk, reluctance to move, stiffness, hyperactivity, hoof disorders and total hoof deterioration, difficulty breathing, cardiomyopathy and other heart issues, collapse, and death. Research has shown the *β*2-AA drug ractopamine, for example, can cause 75 to 90% higher mortality (unexpected deaths) and lameness in cows, especially cows in higher ambient temperatures. Cows fed zilpaterol, another *β*2-AA, also had significantly higher incidences of these health issues, which were sometimes fatal. FDA has this research in its own files. Yet FDA failed to acknowledge or address both the known impacts of beta-agonists that Experior is likely to replicate and the unknowns that distinguish Experior from other beta-agonists.

126. The precise mechanism by which Experior purportedly reduces ammonia gas was also not identified in the studies—and is unknown even to the drug sponsor. This is consistent with a general lack of information about the subtype of beta-agonists to which Experior belongs; *β*3-AAs have been the least studied of the *β*-AAs. *β*3-AA drugs affect adipose, heart/vasculature, urinary bladder, and ovary tissue, but without knowing exactly how the drug functions, the drug sponsor and FDA are necessarily unable to identify and address any side effects the drug may cause. For example, the FOI documents do not explain *how* nitrogen is used more efficiently with the use of Experior, and intimate that the reason is not known. This makes it impossible for FDA to conclude that the drug is safe.

127. FDA also failed to account for how *β*-AAs are processed by different animal breeds, to conclude that effects on cows either could or could not be extrapolated from studies on other animals. At least one study indicates that there is a significant difference in how various animals respond to *β*-AAs, indicating a need for further research on the effects of Experior on cows.

128. In so doing, FDA ignored evidence in its own files about the negative animal health effects of beta-agonists.

129. At best, it is unknown what Experior's effects on cows might be; at worst, it will have severe, unintended negative effects.

Drug Effectiveness in Target Animals

130. The FDCA requires FDA to refuse any new animal drug application that has not been shown to be effective in target animals.

131. The FOI Summary readily admits that reliable predictions of the effectiveness of the drug at a herd, farm, or larger scale "cannot be made."

132. The FOI Summary illustrates that ammonia gas emissions vary depending on the size of the animal, the quantity of feed consumed, and other factors.

133. The FOI Summary also illustrates that a certain amount of data manipulation was necessary to achieve the desired outcome on effectiveness. The studies on which FDA relied were all done on relatively small sample sizes, then only a post hoc Bonferroni correction—a multiple-comparison correction used when several dependent or independent statistical tests are being performed simultaneously—resulted in a statistically significant decrease in ammonia levels with increased dosage. Only by using p-values instead of Confidence Intervals and eliminating two "outlier" groups did the studies result in the reported decrease in ammonia.

134. In short, Experior has not been shown to be effective.

Effects on the Environment

135. Experior is purported to reduce ammonia emissions from cow manure. Urine and fecal material, individually, emit minimal amounts of ammonia; it is the physical process of combining urine and feces after deposition on a surface that results in ammonia volatilization (ammonia gas). Yet Experior itself will enter the environment through manure, and FDA fails to identify several known risks of environmental contamination due to CAFO manure management practices that will enable Experior to permeate the environment.

136. The EA states that Experior will only enter the environment through land application of manure and corresponding runoff and will not contaminate groundwater. It fails to consider that manure can be stored in unlined lagoons that are susceptible to leakage, overflow,

or rupture, any of which could lead to groundwater and soil contamination. It also fails to account for uneaten medicated feed which could also contaminate groundwater and soil.

137. The EA further relies on severely underestimated numbers with regard to daily manure production but fails to explain the basis of such numbers beyond obliquely stating that the "[v]alue is consistent with values typically used in environmental risk assessments."

138. The Experior FONSI also failed entirely to consider alternatives to the proposed action, as NEPA requires. FDA thus failed to acknowledge that it could have denied the application or placed strict conditions on Experior's use to avoid the substantial environmental burden imposed by an additional, widespread approval of a new beta-agonist throughout the United States.

139. FDA's denial of ALDF's Petition also erroneously states that if more cows were to be confined and produce a higher volume of manure, it would result in lower concentrations of Experior in the environment. The concentration in the manure would be lower for each animal if total quantity of excreted drug is constant, but the total concentration in the environment will not necessarily be lower since this is dependent on the total number of animals given the drug, the density of animals in the environment, and manure management practices—not only on the concentration in the manure.

140. FDA also assigns any responsibility for poor manure management conditions to the EPA. However, FDA, not EPA, has a duty to analyze this eventuality before approving a new animal drug. Manure mismanagement, and environmental contamination from even "proper" manure management, is common; FDA failed to analyze this as part of its approval, relying improperly on EPA's role in enforcing federal laws designed to protect navigable waters. Moreover, EPA notoriously underregulates the CAFO industry. As early as 1994, EPA acknowledged that agriculture is the leading contributor to water quality impairments, and that pollution associated with animal feeding operations degrades the quality of waters and threatens drinking water sources. In 2012, the EPA estimated that there may be a total of 18,540 animal confinement facilities that meet the federal Clean Water Act's CAFO definition, 40 C.F.R. § 122.23(b)(2), but just 7,642 of those facilities maintained Clean Water Act permits. As of

2018, only 6,597 were permitted.[15] Accordingly, the majority of CAFOs may be discharging manure contaminated with Experior and other animal drugs in open violation of state and federal law. FDA failed to consider this.

141. FDA further accepted the drug sponsor's assertion that very little Experior would be excreted by cows unchanged and that there are no deleterious metabolites, despite this statement being largely unsubstantiated and not at all congruous with the excretion rates of other beta-agonists.

142. FDA also failed to consider the impacts of Experior on aquatic species and other threatened and endangered wildlife. The drug approval documents contain limited research on the effects of Experior on aquatic species, including invertebrates, except for one small study on rainbow trout, noted in the FOI Summary. They also fail to address that reduced growth and number of viable fish eggs and other deleterious effects have been reported with other β-AAs in water, or that there has been virtually no research done on the effects of β-AAs on bees or other pollinators.

143. Finally, FDA failed to account for unknowns. As described above, the precise mechanism by which Experior purportedly reduces ammonia gas was not identified in the new drug approval application and is unknown even to the drug sponsor; the FOI documents do not explain *how* nitrogen is used more efficiently with the use of Experior, and intimate that the reason is not known. Without knowing exactly how the drug functions, the drug sponsor and FDA are necessarily unable to identify and address any environmental side effects the drug may cause, including any possible increase in other pollutants caused by or associated with the claimed reduction in ammonia.

144. In so doing, FDA ignored evidence in its own files about the negative environmental effects, and particularly cumulative effects, of beta-agonists.

//

[15] EPA, NPDES CAFO Regulations Implementation Status Reports – National Summary, Endyear 2018, https://www.epa.gov/npdes/npdes-cafo-regulations-implementation-status-reports (last visited June 4, 2020).

FIRST CLAIM FOR RELIEF

FDA unlawfully denied Plaintiff ALDF's Petition

1. Plaintiffs reallege and incorporate by reference all prior paragraphs, as though fully alleged herein.

2. FDA's regulations allow any interested person to submit an administrative request to stay an action. 21 C.F.R. § 10.35.

3. The Commissioner shall grant a stay in any proceeding if all of the following apply: (1) the petitioner will otherwise suffer irreparable injury; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting a stay; and (4) the delay resulting from the stay is not outweighed by public health or other public interests. *Id*. § 10.35(e)(1).

4. A timely petition to stay exhausts administrative remedies. *Id*. § 10.45(c).

5. Plaintiff ALDF filed a timely Petition illustrating (1) that it would suffer irreparable harm by FDA's failure to stay the Experior approval pending further review; (2) that its petition was in good faith and not frivolous; (3) that ensuring target animal safety and effectiveness and compliance with environmental laws are sound public policy grounds that support a stay; and (4) that any delay is not outweighed by public health or other public interests.

145. FDA erroneously denied ALDF's Petition.

146. In so doing, FDA acted in violation of § 706(2) of the APA because it "relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Assoc. v. State Farm Mutual Auto. Ins. Co*., 463 U.S. 29, 43 (1983).

6. FDA's denial of a petition to stay, and specifically ALDF's Petition, is final agency action subject to judicial review under the APA. *See* 5 U.S.C. § 704.

7. FDA's failure to comply with the FDCA and the APA harms Plaintiffs and their members' interests.

SECOND CLAIM FOR RELIEF

FDA unlawfully approved Experior in violation of the FDCA and the APA

8. Plaintiffs reallege and incorporate by reference all prior paragraphs, as though fully alleged herein.

9. The FDCA deems new animal drugs "unsafe" unless FDA has approved a new animal drug application for the drug and its use conforms to its labeling and the conditions of the approved application. 21 U.S.C. § 360b(a)(1).

10. The FDCA requires FDA to refuse any new animal drug application where it has not been shown to be both safe and effective. *Id*. § 360b(b).

11. FDA approved Experior without showing it to be either safe or effective.

12. FDA's 2018 approval of Experior is a final agency action subject to judicial review under the APA. *See* 5 U.S.C. § 704. ALDF's timely Petition exhausted its administrative remedies. *See* 21 C.F.R. § 10.45(c).

13. In approving Experior, FDA violated § 706(2) of the APA because it "relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Assoc. v. State Farm Mutual Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

14. Its decision to approve Experior even though the new animal drug application failed to meet the requirements of the FDCA also exceeded its statutory authority. 5 U.S.C. § 706(2).

15. FDA's failure to comply with the FDCA and the APA harms Plaintiffs and their members' interests.

THIRD CLAIM FOR RELIEF

FDA unlawfully approved Experior in violation of NEPA and the APA

16. Plaintiffs reallege and incorporate by reference all prior paragraphs, as though fully alleged herein.

17. FDA's approval of Experior is a final, major federal action that requires compliance with NEPA and is subject to judicial review under the APA. 5 U.S.C. § 704.

18. ALDF's timely petition to stay FDA approval of Experior exhausts administrative remedies. *See* 21 C.F.R. § 10.45(c).

19. NEPA requires agencies to explain why a proposed action will not have a significant effect on the human environment. 40 C.F.R. § 1508.27.

20. FDA did not take the requisite "hard look" at the environmental impacts of its decision to approve Experior, failed to consider the potential national human health and safety impacts of its action despite significant risk and concern of such impacts, and never considered any of the factors required by agencies to determine the intensity of a proposed action's environmental impacts.

21. NEPA requires agencies to "rigorously explore and objectively evaluate" any reasonable alternatives to the proposed action. *Id.* § 1502.14(a); 42 U.S.C. § 4332(2)(E). The Experior FONSI failed entirely to consider alternatives to the proposed action.

22. CEQ regulations also require an agency to consider the direct, indirect, and cumulative impacts of a proposed action's impact on the environment. *Id.* § 1508.8. FDA failed entirely to consider cumulative impacts.

23. NEPA requires public participation in all aspects of the NEPA process. 42 U.S.C. § 4332(2)(C); 40 C.F.R § 1500.1(b). This complements the FDCA's requirement to publish notice of new drug approvals in the Federal Register, 21 U.S.C. § 360(i).

24. FDA undertook the approval of Experior, the Experior EA, and FONSI without any public participation, and only published notice of its decision after the point at which the public could meaningfully contribute to the process.

25. FDA's decision to approve Experior was therefore arbitrary and capricious, an abuse of discretion, and otherwise not in accordance with NEPA, 42 U.S.C. § 4332, and without observance of procedures required by law in violation of the APA, 5 U.S.C. §§ 701-706, and must be set aside.

26. FDA's failure to comply with NEPA and the APA harms Plaintiffs and their members' interests.

REQUEST FOR RELIEF

WHEREFORE, Plaintiffs request that the Court:

1. Declare that FDA's failure to comply with the FDCA in approving Experior violates the FDCA, the APA, and FDA regulations;

2. Declare that FDA's failure to comply with NEPA before approving Experior violates NEPA and the APA;

3. Vacate FDA's decision to approve Experior unless and until it complies with the FDCA, NEPA, and the APA;

4. Issue preliminary and permanent injunctive relief barring the use of Experior until FDA complies with the FDCA, NEPA, and the APA;

5. Award Plaintiffs fees, expenses, and costs pursuant to the Equal Access to Justice Act, 28 U.S.C. § 2412(d); and

6. Grant Plaintiffs such further relief as is proper, just, and equitable.

DATED: June 4, 2020 in San Francisco, California.

Signed: /s/ *Cristina R. Stella*

CRISTINA R. STELLA (State Bar No. 305475)
Animal Legal Defense Fund
525 E. Cotati Avenue
Cotati, CA 94931
T: (707) 795-2533 ext. 1055
cstella@aldf.org

PAIGE M. TOMASELLI (State Bar No. 237737)
The Law Office of Paige Tomaselli
P.O. Box 71022
Richmond, CA 94807
T: (619) 339-3180
paige@tomasellilaw.com