Via Regulations.gov

December 7, 2023

Dockets Management Staff (HFA–305),
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2023–N–4742 for ''Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing.''

We, the undersigned organizations appreciate the opportunity to comment upon the Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed.[1] We support the Food and Drug Administration's (FDA's) plan to withdraw approval of these new animal drug applications and ask that the agency also deny the drug sponsor's request for hearing.

Section 512(d)(1)(I) of the Federal Food, Drug, and Cosmetic Act—the so-called "Delaney Clause"—requires that no residue of a carcinogenic drug can be found in any edible portion of an animal after slaughter.[2] The DES proviso creates an exception to the Delaney clause allowing the use of a cancer-causing drug in food animals when the FDA approves a method to test for residues that ensures there is no significant risk of cancer from carcinogenic residues in animal products. The FDA has given the drug sponsor almost 20 years to submit a residue detection method that meets regulatory requirements to ensure the safety of this product, but the sponsor has not done so—probably because no such residue detection method exists. Accordingly, the FDA should immediately withdraw approval of the new animal drug applications.

We also ask that the FDA deny the drug sponsor's request for a hearing. However, if the FDA grants the drug sponsor a hearing, we ask that the FDA suspend the approval of the carbadox new animal drug applications, as its continued use is clearly unsafe since there is no approved method to test that the drug is being used safely, and the labeled withdrawal period is no longer valid since it is based upon the revoked method. In addition, available data shows that unsafe levels of desoxycarbadox (DCBX) and other carcinogenic residues can be present in pork products when carbadox is used according to the approved label.

The FDA has deferred to the interests of the drug sponsor for far too long; it is now time for the agency to give the same consideration to consumers, workers, the environment and environmental justice communities, the goals of the Biden Administration, and the FDA's own public health mission and ban

[1] 88 FR 76756: 76756-76760; https://www.federalregister.gov/documents/2023/11/07/2023-24547/phibro-animal-health-corp-proposal-to-withdraw-approval-of-new-animal-drug-applications-for-carbadox

[2] 21 U.S.C. § 360b(d)(1)(I).

this dangerous drug. To do otherwise would be arbitrary, capricious, an abuse of discretion, and otherwise contrary to law.

The FDA has ignored its public health mission for way too long when it comes to carbadox.

Since 1972, the FDA has allowed the use of a cancer-causing drug to be added in pig feed with no veterinary oversight and no limit on how long the drug can be used, except for a withdrawal period that is based upon flawed data. This is the last of the animal drugs misguidedly approved under the DES proviso. The FDA withdrew approval of diethylstilbestrol, the namesake of the DES proviso, in 1979, and nitrofurans in 1991.[3] Both drugs were withdrawn in contested withdrawal hearings when it became clear that continued use of the drugs were unsafe.

In 1998, at the request of the drug sponsor, the FDA ignored its own rules to approve a new residue detection method for carbadox and shortened the withdrawal period from 70 to 42 days. The agency failed to apply regulations implementing the DES proviso of the Delaney clause that require that any marker residue be linked to the residues of carcinogenic concern (21 C.F.R. § 500.84). These FDA rules require that the drug sponsor identify a specific marker residue with a known relationship to all carcinogenic residues that can be used to identify whether the cancer-causing residues are present in animal products at a level below that which creates a significant risk of cancer in consumers. The drug sponsor did not identify the relationship between the marker residue and the other residues as required by the regulations. The sponsor instead provided data, later found to be incorrect, showing that there were no detectable residues other than the proposed marker the non-carcinogenic quinoxaline-2-carboxylic acid (QCA) three days after the last administration of the drug to pigs. Based on this, the FDA approved QCA as the marker residue at 30 parts per billion or ppb. The assumption was that if QCA was low enough (30 ppb), then there would not be dangerous levels of other cancer-causing residues since QCA stayed in the tissues longer than any other residues. The FDA at that time had identified a "safe" amount of the other carcinogenic residues allowed in pork products. Compounding this problem, the FDA further failed to require that the method be published in the Code of Federal Regulations under section 21 CFR Part 500 Subpart F as required by regulation.[4]

Not much later, in 2003, the drug sponsor submitted additional data not shared with the FDA to the Joint FAO/WHO Expert Committee on Food Additives (JECFA) showing that a known cancer-causing residue desoxycarbadox (DCBX) could be detected for 15 days, five times longer than the three days on which the residue detection method approved by the FDA was based. In addition, the additional data provided by the drug sponsor to JECFA showed that when QCA was detected at a level below 30 ppb—the level for which carcinogenic residues should not be present at dangerous levels under the FDA-approved method—the cancer-causing residue DCBX could be found in pork tissues above the FDA identified safe level by a factor of 4-5.[5] In short, within five years of requesting that the FDA approve its new detection

[3] There is one other drug ingredient, N-methyl-2-pyrrolidone, that is used as a solvent in some formulations of injectable animal drugs that is regulated under the DES proviso as a carcinogen.

[4] This section summarizes information in the FDA Final Order Revoking the Approved Method, 88 FR 76760: 76760-76770; https://www.federalregister.gov/documents/2023/11/07/2023-24548/phibro-animal-health-corp-carbadox-in-medicated-swine-feed-revocation-of-approved-method

[5] CARBADOX (addendum) (JECFA Food Additives Series 51). https://inchem.org/documents/jecfa/jecmono/v51je05.htm (accessed 2023-12-07).

method, the drug sponsor provided additional data *to a separate governing body* showing that the method did not work—i.e., pork that would be considered safe by the method could contain cancer-causing residues above the safe level determined by FDA.

The sponsor waited until 2005, two years later, to provide the FDA with a summary of the data it provided to JECFA and then another 6 years on top of that, 2011, before it provided the FDA with the complete set of data, and only then provided the data following an order by the agency. The sponsor has known since at least 2003 (and the FDA has known since at least 2005) that the residue detection method used to "ensure that residues of carcinogenic concern in edible tissues will not exceed concentrations that represent no significant increase in the risk of cancer to humans"[6] do not provide the needed certainty to protect consumers from a significant increase in the risk of cancer. Since 2005, the FDA has provided the drug sponsor the opportunity to propose a method and supporting data to provide the needed certainty. The drug sponsor has not done so. During this time, the FDA and the drug sponsor have knowingly allowed U.S. consumers to be exposed to a "significant increased risk of cancer."

Carbadox use is growing expanding the risk

Over this period, the use of carbadox has become much more widespread. In 2000, 23% of sites with nursery pigs used the drug.[7] In 2017, use had increased to at least 48% of sites[8] and preliminary data show that 59% of sites used the drug in 2021.[9] The latest increase is likely influenced by the FDA action of placing new restrictions on the use of medically important antibiotics in 2017 while also considering carbadox a non-medically important antibiotic, even though carbadox also likely contributes to the problem of antibiotic resistance.[10] There is no evidence that swine dysentery, *Salmonella choleraesuis*, and increasing pig weight gain and feed efficiency, the three indications for which carbadox can legally be used, would justify this level of use.

Carbadox use also harms workers, the environment, and environmental justice communities

In addition to the harm to consumers, carbadox use also threatens the health of workers who are forced to handle materials contaminated by carbadox and to breathe air contaminated by carbadox dust. Specifically, carbadox poses allergen and genotoxicity hazards to the farm and feed mill workers who are exposed to feed and feed dust containing the drug.[11]

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[6] 88 FR 76759.

[7] USDA. Part II. Reference of Swine Health and Management in the United States, 2002. USDA:APHIS:VS, CEAH, National Animal Health Monitoring System. March 2002. https://www.aphis.usda.gov/animal_health/nahms/swine/downloads/swine2000/Swine2000_dr_PartII.pdf

[8]USDA. Antimicrobial Use and Stewardship on U.S. Swine Operations, 2017. USDA:APHIS:VS, CEAH, National Animal Health Monitoring System. May 2019. https://www.aphis.usda.gov/animal_health/nahms/amr/downloads/amu-swine.pdf

[9] Personal communication from Chelsey Shively and NAHMS staff, October 4, 2023.

[10] Bearson, S. M. D. Salmonella in Swine: Prevalence, Multidrug Resistance, and Vaccination Strategies. Annual Review of Animal Biosciences 2022, 10 (1), 373–393. https://doi.org/10.1146/annurev-animal-013120-043304. 4

[11] Baars, A.J. Carbadox - An Evaluation, Report 97.17 April 1997. https://edepot.wur.nl/264615.

Carbadox has been detected in surface waters likely entering the water after being excreted in pig waste or through improper disposal [12], further threatening the communities and environments in which carbadox is administered, which tend to be low-income and BIPOC.[13] This violates the Biden Administration's environmental justice goals. President Biden has strengthened the executive branch's previous environmental justice commitments. In 1994, President Clinton issued Executive Order 12,898, Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations.[14] This order directed all federal agencies to make environmental justice part of their mission and to identify and address the disproportionate environmental and health effects of their activities on BIPOC and low-income communities.[15] In January 2021, President Biden issued Executive Order 13,990, Protecting Public Health and the Environment and Restoring Science To Tackle the Climate Crisis.[16] This order "highlights the need to . . . prioritize environmental justice."[17] The Biden Administration further demonstrated its commitment to and prioritization of addressing historic environmental injustice in April 2023, when the White House issued Executive Order 14,096, Revitalizing Our Nation's Commitment to Environmental Justice for All.[18] This order "further embed[s] environmental justice into the work of federal agencies to achieve real, measurable progress that communities can count on."[19]

The FDA should deny any hearing request by the sponsor that is not based upon the submission of a method that ensures that the use of carbadox does not lead to cancer-causing residues in pork.

The FDA has ignored the interests of consumers, workers, and environmental justice communities for too long. The agency has for almost 20 years given the drug sponsor the opportunity to address the safety problems with its product, but the drug sponsor has failed to do so. As clearly laid out in the revocation of the method and the NOOH, there are no substantial questions of fact. The approved method was

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[12] Minnesota Department of Public Health. Carbadox Screening. July 2016. https://www.health.state.mn.us/communities/environment/risk/docs/guidance/dwec/screening/carbadox.pdf

[13] Factory farms where the vast majority of pigs are raised—and where carbadox is administered—are disproportionately sited in environmental justice communities. *See, e.g.*, *See* Letter from Lilian S. Dorka, Director, Env't Protect. Agency External Civil Rights Compliance Office, to William G. Ross, Jr., Acting Secretary, North Carolina Dep't of Env't Quality (Jan. 12, 2017), https://perma.cc/EJU5-UHUW (describing discriminatory health and quality of life impacts from pig and bird CAFOs); Steve Wing and Jill Johnston, *Industrial Hog Operations in North Carolina Disproportionately Impact African-Americans, Hispanics and American Indians* (Aug. 29, 2014), https://perma.cc/K4EJ-6QZX; Kelley J. Donham et al., *Community Health and Socioeconomic Issues Surrounding Concentrated Animal Feeding Operations*, 115 ENVTL. HEALTH PERSP. 317 (2007), https://perma.cc/8PSV-R5NU; Steve Wing et al., *Environmental Injustice in North Carolina's Hog Industry*, 108 ENVTL. HEALTH PERSP. 225 (2000), https://perma.cc/8SED-X6PY.

[14] Relevant communities include "minority populations and low-income populations in the United States and its territories and possessions." Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations, Exec. Order No. 12,898, 3 C.F.R. 859 (1995), reprinted as amended in 42 U.S.C. § 4321 (1998).

[15] *See id.*

[16] Protecting Public Health and the Environment and Restoring Science To Tackle the Climate Crisis, Exec. Order No. 13,990, 86 Fed. Reg. 7,037 (Jan 25, 2021).

[17] *Climate Change Coordination*, DEP'T OF THE INTERIOR, https://perma.cc/A5NY-K6V2 (last visited May 3, 2023).

[18] Revitalizing Our Nation's Commitment to Environmental Justice for All, Exec. Order No. 14,096, 88 Fed. Reg. 25,251 (Apr. 21, 2023).

[19] *Fact Sheet: President Biden Signs Executive Order to Revitalize Our Nation's Commitment to Environmental Justice for All*, THE WHITE HOUSE (Apr. 21, 2023), https://perma.cc/57G8-MY5M.

based on incorrect assumptions that have been known to be wrong since 2003, and the sponsor has not provided an alternative method that meets the legal requirements designed to protect consumers from exposure to carcinogens. The FDA must deny the hearing request.[20]

If the FDA allows a hearing to move forward, the agency should suspend the approval of the carbadox new animal drug applications due to the imminent hazard to consumers of pork from unsafe residues and to workers, the environment, environmental justice communities, from exposure to the drug through contact with feed, feed dust, and to surface waters contaminated by pig manure.

The evidence is clear. The residue detection method approved in 1998 did not meet the FDA's regulatory requirements for a known carcinogen and puts consumers at significant risk of cancer since DCBX, a known carcinogen, can be detected in pork products at dangerous levels even when the method determined the product was safe. The method created a false sense of safety and that method has now been revoked.

In addition, the labeled withdrawal period of 42 days, the primary tool for assuring the human food safety of animal drugs for use in food-producing animals, is based on the residue detection method that was revoked and is based on incorrect assumptions. The 42 days is based on the assumption that no carcinogenic residues could be detected in pig tissue more than three days after withdrawal of the drug, but we now know that carcinogenic residues can be detected at least 15 days after withdrawal.

The continued use of carbadox in pigs cannot be considered safe when there is no method to determine whether it has been used according to label, and even if there were a method, the label itself is compromised since the withdrawal period is based on invalidated data. Therefore, we ask that the Commissioner suspend approval of carbadox as an imminent hazard during any hearing proceedings because the continued use of the drug without a residue detection method and with a non-protective withdrawal period is clearly unsafe.[21]

While the lack of a meaningful withdrawal period is sufficient to make the drug unsafe, other approved conditions of its use also increase the risk. The use of carbadox does not require veterinary oversight and has no duration limit. Unsurprisingly, given the widespread use and lack of veterinary oversight, it has been the most detected residue in random sampling of pork with residue levels found to be many orders of magnitude higher than what was allowed under the method that has been revoked.[22] The revoked method itself was not sufficiently protective so these violations represent an even greater risk to consumers, 2019 and 2020, the levels of residues detected by the U.S. Department of Agriculture (USDA) in pork products were 1,300 to 12,000 times the legal limit. These levels were so high that signing organization Food Animal Concerns Trust checked with the USDA because it thought they might be in error, but the USDA confirmed that the findings are correct.[23]

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[20] *See, e.g.*, *John D. Copanos & Sons, Inc. v. Food & Drug Admin.*, 854 F.2d 510, 518 (D.C. Cir. 1988) ("It is well settled that [the FDCA regulation allowing an opportunity for hearing] does not guarantee the applicant a hearing in all circumstances; the agency may by regulation provide for summary withdrawal of approvals when there is no genuine and substantial issue of fact that requires a hearing.") (citations and quotations omitted).

[21] *See* 21 U.S.C. § 360b(e)(1).

[22] Kleven, M. Poisonous Pork: Carbadox Residue Violations in USDA Testing. August 2023. https://www.foodanimalconcernstrust.org/s/Poisonous-Pork_USDA-violations-of-Carbadox-Report_Aug-2023_FINAL.pdf

[23] Email from USDA Food Safety Inspection Service (FSIS) 8/25/23 and virtual meeting with FSIS staff 10/27/23.

Conclusion

The FDA has allowed the use of this dangerous animal drug for too long, despite knowing that the data on which its approved conditions of use are based were flawed. The agency has given more than sufficient time to the drug sponsor to address these problems, and the drug sponsor cannot. The FDA should act now and stop its incessant delay. The agency must withdraw approval of the carbadox new animal drug applications and deny the request for hearing. To do otherwise would be arbitrary, capricious, an abuse of discretion, and otherwise contrary to law.

Animal Legal Defense Fund

Center for Biological Diversity

Earthjustice

FarmSTAND

Food Animal Concerns Trust

Food and Water Watch

Humane Society Legislative Fund

Humane Society Veterinary Medical Association

Kewaunee Cares

Mercy For Animals

Socially Responsible Agriculture Project

The Cornucopia Institute

The Humane Society of the United States

Waterkeeper Alliance