November 3, 2023

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850 Tenth Street, NW
Washington, DC 20001-4956

Re: Docket No. FDA-2020-P-2313

Dear Dr. Perron:

This is a final response to the stay petition (FDA-2020-P-2313) you filed with the Food and Drug Administration (FDA) on November 17, 2020, on behalf of Phibro Animal Health Corporation, concerning the New Animal Drug Applications (NADAs) for carbadox, a carcinogenic new animal drug used in swine feed.[1]

In your petition, you request that FDA stay the effective date of any final order revoking the approved carbadox regulatory method. Under 21 CFR 10.35(e), FDA shall grant a stay if all of the following four factors apply: The petitioner will otherwise suffer irreparable injury, the petitioner's case is not frivolous and is being pursued in good faith, the petitioner has demonstrated sound public policy grounds supporting the stay, and the delay resulting from the stay is not outweighed by public health or other public interests. FDA also may grant a stay if it is in the public interest and in the interest of justice.

You state that without a stay, Phibro and its customers would suffer irreparable harm. Petition at 10. You also state that a stay is necessary to avoid piecemeal legal challenges to interrelated issues, that Phibro is challenging this approach non-frivolously and in good faith, and that continued sale of carbadox supports animal health and serves the public interest in preventing antimicrobial resistance because alternatives to carbadox are antimicrobials of importance to human medicine. Petition at 12-16.

After reviewing your petition for a stay, FDA has determined that a stay is not in the public interest and is not warranted under three of the four factors in 21 CFR 10.35(e).[2]

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[1] On May 18, 2021, FDA tentatively replied to your citizen petition and explained that the agency needed additional time to respond and that for administrative efficiency FDA had assigned two distinct docket numbers to your request. Docket Number FDA-2020-P-2312 was assigned to the request for FDA to "refrain from finalizing, and withdraw, the Proposed Order" and Docket Number FDA-2020-P-2313 was assigned to the request to "stay the effective date of any final order revoking the carbadox regulatory method pending the final resolution of any future proceeding to withdraw approval for the carbadox NADAs."

[2] Because three factors weigh against a stay and all four factors must be present for a mandatory stay, we did not need to reach a determination on the other factor: whether Phibro's request is not frivolous and is being pursued in good faith.

Phibro will not suffer irreparable harm because the final order, which will be publicly available in the Federal Register, does not prevent Phibro from marketing carbadox. In addition, public policy supports finalizing the order because Congress has mandated that FDA ensure no carcinogenic residues persist in edible tissues. Finally, further delay is not warranted when Phibro has had over a decade to conduct the necessary studies to identify a marker residue in a known relationship with the residue of carcinogenic concern.

1. *The final order does not cause irreparable harm to Phibro because Phibro can continue to market carbadox*

Your petition asserts that the final order "would cause Phibro irreparable harm in the form of millions of dollars in lost sales, reputational harm, and deployment of additional, otherwise unnecessary resources to address confusion in the marketplace regarding carbadox's regulatory status and safety." Petition at 10. However, as discussed in the response to FDA-2020-P-2312, Phibro remains able to market carbadox, even after issuance of a final order revoking the approved method, so any change in sales would be based on anticipation that carbadox will be withdrawn following the notice of opportunity for a hearing.[3] Given that the alternative process Phibro proposes (addressing the adequacy of the approved method at a hearing) would raise the same legal and scientific issues about the adequacy of the method, it is unclear how a change in process, but not a change in substance, would reduce costs to Phibro or result in greater clarity in the marketplace. The uncertainty about carbadox's regulatory status stems from research showing that carcinogenic residues persist longer than previously known. Staying the final order would not change public knowledge about these concerns and therefore appears unlikely to address Phibro's financial or reputational concerns.

Furthermore, irreparable harm is considered within the context of a company's overall financial health and requires evidence that lost profits are "certain" or "great." *Alcresta Therapeutics, Inc. v. Azar*, 318 F. Supp. 3d 321, 327 (D.D.C. 2018) (holding that drug company did not show irreparable harm because there was no evidence that lost profits were "certain" or "great"). Your petition generally estimated "millions of dollars in lost sales," Petition at 10, but publicly available information shows that carbadox is a small portion of Phibro's overall sales: Phibro reported net sales of $978 million for the fiscal year ending June 30, 2023, and Mecadox (carbadox) sales of $20 million during that time.[4] Even assuming no sales of Mecadox after issuance of a final order, this would represent about only a 2% loss of Phibro's total sales. This outcome also seems unlikely in light of Phibro's statement that a survey of veterinarians in 2020 who influence the

[3] While you also argue that an order revoking the approved method may be viewed "as a *de facto* determination that carbadox is unsafe" and thus adulterated under the Federal Food, Drug, and Cosmetic Act (FD&C Act), Petition at 11-12, up and until culmination of the administrative proceeding noticed by the 2023 Notice of Opportunity for Hearing (NOOH) that will shortly be available in the Federal Register, CVM will not take the view that carbadox is adulterated by reason of it not having an approved method.

[4] U.S. Securities and Exchange Commission, Form 10-k for Phibro Animal Health Corporation for the fiscal year ended June 30, 2023, available at https://www.sec.gov/ix?doc=/Archives/edgar/data/1069899/000155837023015357/pahc-20230630x10k.htm.

health decisions of 94.9 million pigs found that these veterinarians value the benefits provided by carbadox and see other alternatives as inferior. Petition, Exhibit A at 3-5. Given these reported statements from veterinarians who strongly prefer carbadox, it seems counter-intuitive to assume that they would stop prescribing carbadox while it remains legal to do so.

2. *Phibro has not demonstrated sound public policy grounds supporting the stay*

    a. *The public interest is served by ensuring no carcinogenic residues persist in edible tissues, as required by the Delaney Clause and DES Proviso*

Although your petition asserts that carbadox is safe, the legal standard for carcinogenic new animal drugs is stricter than the general safety clause that applies to all new animal drugs. Before approving a new animal drug for use in food-producing animals, FDA determines that the drug is safe for human consumers, which means a "reasonable certainty of no harm." See Guidance for Industry #3, "General Principles for Evaluating the Human Food Safety of New Animal Drugs Used in Food-Producing Animals" (May 2022).[5] For carcinogenic new animal drugs used in animal food, however, it is not enough to show reasonable certainty of no harm. Instead, Congress also chose to require a regulatory method for determining that no residue of the carcinogenic drug will be found in any edible tissues or foods from a treated animal. 21 U.S.C. 360b(d)(1)(I). FDA cannot accept a finding that a residue is present, but below the "no significant increase in risk to the human consumer" level, as satisfying the statutory requirement of "no residue."[6]

Based on the available evidence, FDA cannot conclude that carbadox residues have reached a concentration representing "no significant increase in risk to the human consumer" *or* "no residue" even at 70 days post-dosing, the last time-point measured in the data provided for the 1998 supplemental approval. For carbadox, the concentration of the residue of carcinogenic concern that represents "no significant increase in the risk of cancer to the human consumer," 21 CFR 500.82(b) (defining S_m), is 0.915 parts per billion (ppb). The residue of carcinogenic concern is found by measuring all carbadox residues and then subtracting the residues known to be noncarcinogenic.[7] 21 CFR 500.82 (defining residue of carcinogenic concern). "No residue" means the marker residue depletes below a method's limit of detection in accordance with the statutory requirement that "no residue of such drug will be found . . . by methods of examination prescribed or approved by the Secretary by regulations." 21 U.S.C. 360b(d)(1)(I); 21 CFR 500.82(b). The data from the 1998 supplemental approval showed a concentration of 11.98 ppb of

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[5] https://www.fda.gov/media/70028/download.

[6] DOJ, Mem. Op. for the Assistant Administrator & Gen. Counsel EPA & Gen. Counsel DHHS (Oct. 13, 1995), https://www.justice.gov/d9/olc/opinions/1995/10/31/op-olc-v019-p0247_0.pdf.

[7] According to the 1998 Freedom of Information (FOI) Summary, quinoxaline-2-carboxylic acid (QCA) and methyl carbazate are noncarcinogenic metabolites of carbadox. FDA, FOI Summary, NADA 041-061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval January 30, 1998, at 8, available at https://animaldrugsatfda fda.gov/adafda/app/search/public/document/downloadFoi/308.

carbadox residues at 70 days post-dosing after subtracting the concentration of noncarcinogenic quinoxaline-2-carboxylic acid (QCA).[8, 9] This concentration is 13 times greater than the value that represents no significant increase in the risk of cancer to the human consumer (0.915 ppb). Without knowing the concentration of the marker residue (R_m) when the residue of carcinogenic concern depletes to 0.915 ppb, it is impossible to conclude that a method for detecting carbadox residues satisfies the statutory and regulatory requirements. Once the R_m is known, CVM could set an appropriate withdrawal period to ensure no carcinogenic residues persist in edible tissues.

In addition, calculations provided by Phibro illustrate that there could be a significant amount of time between when the concentration of residue of carcinogenic concern is 0.915 ppb ("no significant increase in risk to the human consumer") and when the residue is not detectable ("no residue"). According to calculations by one of Phibro's experts, desoxycarbadox (DCBX), a carcinogenic metabolite of carbadox, depletes to a concentration of 0.915 ppb at approximately 23 days post-dosing and reaches the 0.015 ppb detection limit for the Canadian Food Inspection Agency (CFIA) method of testing DCBX at 75 days post-dosing.[10] In other words, this estimate concluded that it took 52 days for a specific residue to deplete from 0.915 ppb to that method's limit of detection. By comparison, the current withdrawal period for carbadox is 42 days, which means swine may be lawfully slaughtered beginning 42 days after the animal last consumed carbadox. DCBX is only one part of the residue of carcinogenic concern for carbadox, so this analysis is insufficient to address the residue of carcinogenic concern, but it does highlight the importance of data that would enable FDA to conclude when the residue of carcinogenic concern depletes to a level representing "no significant increase in risk to the human consumer" and when it depletes to the level of no detectable residue.

Although your petition asserts that "there is not a single known case of carbadox causing cancer in swine or humans" since its initial 1972 approval, Petition at 2, this statement carries little weight because you have not identified, nor are we aware of, any human epidemiology studies to evaluate the association of exposure to carbadox residues from consumption of edible tissues from treated swine and any increase in the risk of cancer in human consumers. This kind of study would be hard to perform because it would be difficult to know the exposure amount, control confounding factors (such as lifestyles, dietary factors, and occupational exposures), and establish an association or lack of such an association.[11] It would be even more difficult to pinpoint the cause of an individual case of cancer. Even when an individual has a significant exposure to a known

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[8] Memorandum to File entitled, "CVM Response to Phibro Animal Health Corporation's September 18, 2020, Comments on CVM's July 20, 2020, Proposed Order to Revoke the Regulatory Method for Carbadox" (Jan. 6, 2022), at 9.

[9] Methyl carbazate was not subtracted from the residue of carcinogenic concern because the sponsor did not provide quantitative measurements for it.

[10] Phibro Animal Health Corporation's Comments on CVM's July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox, Exhibit 10, Expert Opinion of Robert D. Gibbons Ph.D., at 6, 10.

[11] Memorandum to File entitled, "CVM's Review of Documents Phibro Submitted to Docket No. FDA-2021-N-1326 and Phibro's Presentation at the March 10, 2022, Part 15 Public Hearing" (Oct. 30, 2023).

carcinogen, courts have recognized that other factors could have caused a particular cancer. *See, e.g., In re Hanford Nuclear Reservation Litigation*, 534 F.3d 986, 1010-11 (9th Cir. 2008) (recognizing that factors other than plutonium emissions, such as smoking and genetics, could have caused the plaintiffs to develop cancer even in the absence of any plutonium emissions); *In re Three Mile Island Litig.*, 193 F.3d 613, 643 (3d Cir. 1999) (explaining that establishing causation for a given cancer is extremely difficult), amended, 199 F.3d 158 (3d Cir. 2000).

The carcinogenicity studies of carbadox provided clear evidence that it caused cancer in mice and rats under laboratory conditions.[12] Because "such drug induces cancer when ingested by man or animal," the Delaney Clause applies. 21 U.S.C. 360b(d)(1)(I). Laboratory studies observe an animal for most of its expected lifespan, which is important for a disease like cancer that can take a long time to develop. The carbadox carcinogenicity studies in rats lasted for around 2 years, which represents a significant portion of a rat's expected lifespan. By contrast, most swine are slaughtered before 6 months of age, which represents approximately 2 to 3% of their natural expected lifespan.[13] Given this significant difference in timing, the statements from Phibro, pig producers, and veterinarians that they have not observed cancer in swine treated with carbadox provide little information about any potential long-term cancer risks to swine or human consumers.

Because Congress required an extra margin of safety for carcinogenic animal drugs and food and color additives that could potentially enter the human food supply, FDA has determined that it does not serve the public interest to stay the final order, which will be publicly available in the Federal Register and concludes that the approved method for testing carcinogenic residues does not satisfy the statutory and regulatory requirements. Courts reviewing the language of the anti-cancer Delaney Clause have explained that it does not provide a "de minimis" exception because Congress was particularly concerned with carcinogenic risks compared to other risks and did not grant FDA the administrative discretion that applies to noncarcinogenic risks.[14] *Les v. Reilly,* 968 F.2d 985, 988-90 (9th Cir. 1992) (holding that Delaney Clause applicable to pesticide chemical residues does not contain a "de minimis" exception); *Pub. Citizen v. Young*, 831 F.2d 1108, 1123 (D.C. Cir. 1987) (holding that Delaney Clause applicable to color additives does not contain a "de minimis" exception for carcinogenic dyes that posed a lifetime cancer risk of less than one-in-one million). Although the DES Proviso grants an exception to this otherwise absolute ban on the use of carcinogenic animal drugs, color additives in animal food, and food additives in animal food, it is satisfied only if there is an approved regulatory

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[12] FDA, FOI Summary, NADA 041-061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval January 30, 1998, at 2-7, available at https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/308.

[13] Jagdale A, Iwase H, Klein EC, Cooper DK. Incidence of Neoplasia in Pigs and Its Relevance to Clinical Organ Xenotransplantation. Comp Med. 2019 Apr 1;69(2):86-94, available at https://www ncbi.nlm.nih.gov/pmc/articles/PMC6464082/.

[14] Color additives, food additives, and animal drugs share nearly identical Delaney Clause and DES Proviso language. 21 U.S.C. 348(c)(3)(A) (food additives); 21 U.S.C. 360b(d)(1)(I) (animal drugs); 21 U.S.C. 379e(b)(5)(B) (color additives).

method of testing for residues and a finding of no residue. Because FDA has determined that the approved method does not satisfy this statutory mandate, it is not in the public interest to stay the final order.

b. The strict language of the Delaney Clause and DES Proviso does not allow FDA to weigh cancer risks against other benefits

Your petition asserts that carbadox provides benefits to animal health, the swine industry, and human health and also discusses the economic costs[15] to the swine industry from removal of carbadox from the market. Petition at 10, 14-16. Although you argue that FDA should keep carbadox on the market because of the benefits you identify, Petition at 14, these benefits are not relevant because the FD&C Act bars use of a carcinogenic animal drug in food-producing animals unless there is a finding of no residue in edible tissue from the treated animals. Under "the *per se* rule of the Delaney Clause," FDA may not consider benefits such as "enhancing meat production" through the use of carcinogenic animal drugs. *Hess & Clark, Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975, 993-94 (D.C. Cir. 1974). The relevant provision of the Delaney Clause does not include a cost-benefit analysis but instead is concerned only with ensuring no carcinogenic residues are found in edible tissues.[16] Given this strict and mandatory language, FDA has long maintained that the Delaney Clause requires the agency to ban a carcinogenic animal drug in the absence of an approved method for detecting residues. *See Rhone-Poulenc, Inc., Hess & Clark Div. v. FDA*, 636 F.2d 750, 752 n.2 (D.C. Cir. 1980) (noting FDA's position but declining to decide this legal question and determining that substantial evidence supported banning a carcinogenic animal drug based on the general safety clause). FDA has concluded in the final order, which will be publicly available in the Federal Register, that the Delaney Clause applies here because the DES Proviso is not satisfied. Accordingly, the benefits and costs listed in your petition do not provide public policy grounds for granting a stay of the order revoking the approved method.

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[15] You describe the major drivers of these costs as increase in swine diseases, lack of effectiveness of drugs used in place of carbadox, food safety issues caused by infected pigs, higher pig death loss, reduction in the number of small swine farms, and lower pork quality at higher cost to the consumer. Petition at 10.

[16] Although the D.C. Circuit considered economic benefits in *Rhone-Poulenc, Inc., Hess & Clark Div. v. FDA*, 636 F.2d 750, 754 (D.C. Cir. 1980) with respect to a withdrawal under both the general safety clause and the Delaney Clause, it had earlier made clear that benefits are not considered under the "per se rule of the Delaney Clause." *Hess & Clark*, 495 F.2d at 993. Moreover, later Supreme Court cases have held that congressional silence is not sufficient to support a conclusion that a cost-benefit analysis is required in the plain meaning of words like "public health," "safety," and "health." *Am. Textile Mfrs. Inst., Inc. v. Donovan*, 452 U.S. 490, 510 (1981) ("When Congress has intended that an agency engage in cost-benefit analysis, it has clearly indicated such intent on the face of the statute."); *Whitman v. Am. Trucking Associations*, 531 U.S. 457, 471 (2001); *cf. Michigan v. EPA*, 576 U.S. 743, 752, 755 (2015) ("Read naturally in the present context, the phrase 'appropriate and necessary' requires at least some attention to cost" while a Clean Air Act requirement to set ambient air quality standards at levels '"requisite to protect the public health' with an 'adequate margin of safety[,]' [r]ead naturally, … does not encompass cost; it encompasses health and safety."); *see* Final Decision of the Commissioner in the Withdrawal of the New Animal Drug Application for Enrofloxacin in Poultry, Docket No. 2000N-1571 (July 27, 2005), pages 100-103, available at https://www regulations.gov/document/FDA-2000-N-0109-0137 (part 1) and https://www regulations.gov/document/FDA-2000-N-0109-0136 (part 2).

We note that neither benefits nor risks to the treated animals are at issue with respect to the revocation of the approved method or withdrawal of the carbadox approvals because FDA is not relying on the general safety clause or the provision of the Delaney Clause that prohibits an adverse effect on the treated animals. With respect to *Brachyspira* (which causes swine dysentery) and *Salmonella,* FDA does not dispute that carbadox is effective for these approved indications. But Congress has determined that carcinogenic animal drugs are not permitted in food-producing animals unless there is an approved method that satisfies the statutory requirement of demonstrating "no residue" in edible tissues. Without the data to establish the method required by law, the therapeutic benefits or other potential health benefits of carbadox are legally irrelevant.[17]

Your petition also asserts that the removal of carbadox from the market (something that would not occur until a withdrawal proceeding is final) would lead to "increased swine diseases including those caused by . . . *E. coli* (expected to cost $125 million annually)." Petition at 10. Carbadox is not approved to treat *E. coli*, and extralabel use (a use not in accordance with a drug's approval labeling) is not permitted for a medicated feed, such as carbadox. 21 CFR 530.11(b). Carbadox is approved for sale in combination with oxytetracycline, which is approved to treat *E. coli* in swine. 21 CFR 558.450(e)(3). We assume that your petition is referring to the legal use of this combination product and not to the illegal extralabel use of carbadox to treat *E. coli*. The combination product remains on the market unless and until a withdrawal proceeding is final. Further, because oxytetracycline is not subject to a withdrawal proceeding, it would remain on the market even if carbadox is withdrawn from the market.

Your petition also states that alternatives to carbadox are antimicrobials of importance to human medicine (whereas carbadox is not) and that use of the alternatives could harm human health in the form of increased antimicrobial resistance. Petition at 15. We acknowledge the importance of the judicious use of antimicrobials of importance to human medicine to prevent antimicrobial resistance. But Congress has spoken directly to what is required to use carcinogenic animal drugs in food-producing animals, and there is no exception for animal drugs that provide an alternative to antimicrobials of importance to human medicine. Furthermore, the public harm you identify in your petition (the potential for increased antimicrobial resistance because veterinarians may shift to medically important antimicrobials for use in swine in the absence of carbadox), assumes that veterinarians will not ensure the judicious use of medically important antimicrobials. All antimicrobials of importance to human medicine now require the authorization of a

[17] Under the general safety clause, the typical risk-benefit analysis for a drug compares risks to the patient with therapeutic benefit to the patient. *See United States v. Rutherford*, 442 U.S. 544, 556 (1979) ("[A] drug is unsafe if its potential for inflicting death or physical injury is not offset by the possibility of therapeutic benefit."); *compare* 21 U.S.C. 321(v) *with* 21 U.S.C. 321(p). You state that "[t]he benefits and risks associated with medical products are not limited to those experienced by the individual humans or animals to which they are administered" and that "FDA has the authority and the obligation to consider the overall public health benefits and risks of the products it regulates, including the public health impact of removing a product from the market." Petition at 14. Because overall public health benefits are not relevant under the Delaney Clause, we do not consider them with respect to your request for a stay.

licensed veterinarian.[18] FDA believes that veterinarians have the specialized training and experience to ensure appropriate antimicrobial stewardship.

Accordingly, for the reasons discussed herein, Phibro has not demonstrated sound policy grounds supporting a stay.

3. *Further delay is unwarranted when Phibro has had more than decade to conduct the necessary research and has not done so*

According to your petition, "[t]he Proposed Order comes after Phibro has spent almost a decade attempting to work with CVM to resolve its concerns regarding carbadox and its regulatory method." Petition at 13. It is true that CVM and Phibro spent a decade (from 2005 to 2015) in discussions regarding the data necessary to identify an adequate method, but this factor cuts against further delay because Phibro has had ample time to conduct the necessary studies. Following FDA's receipt in 2005 of the sponsor's summary reports for studies presented at the 2003 Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) meeting that raised concerns about the persistence of carcinogenic carbadox residues, CVM engaged in a decade-long back-and-forth with Phibro about data that would address the relationship between the marker residue and the residue of carcinogenic concern, including meetings, emails, and letters. Given this long history, CVM does not see a need for further delay on this basis.

With respect to the specific design of Phibro's proposed studies, CVM followed its typical process for "protocol concurrence," which allows sponsors to solicit CVM's views on study design before investing time and money carrying out the study. If a sponsor submits a protocol, CVM will "concur" if it determines the study is well designed to address a specific question.[19] Although CVM concurred on a study protocol Phibro submitted in 2006 for a residue depletion study following FDA's Good Laboratory Procedures (GLP), that study was never submitted to CVM. CVM remained willing to review proposed study protocols and provide our feedback, but Phibro did not submit any other protocols until 2015, when it submitted protocols for three studies, one of which was already completed, and two of which were already underway. Because these studies were already completed or in progress, CVM did not review the studies for

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[18] FDA Announces Transition of Over-the-Counter Medically Important Antimicrobials for Animals to Prescription Status, https://www fda.gov/animal-veterinary/cvm-updates/fda-announces-transition-over-counter-medically-important-antimicrobials-animals-prescription-status; FDA Announces Implementation of GFI #213, Outlines Continuing Efforts to Address Antimicrobial Resistance, https://wayback.archive-it.org/7993/20190423131636/https://www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm535154.htm.

[19] CVM, Program Policy and Procedures Manual 1243.4060, Review of Protocols (Aug. 23, 2005), available at https://web.archive.org/web/20100307234608/http://www fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/PoliciesProceduresManual/UCM046863.pdf. This policy and procedures manual has been updated since 2005, but the overall process for requesting protocol concurrence has not changed.

protocol concurrence since it was too late to make changes to the study designs.

Although Phibro states that "CVM first raised questions regarding Phibro's ability to characterize carbadox residues in December 2011," Petition at 13, CVM raised the issue of understanding the relationship between the marker residue and the residue of carcinogenic concern in 2005, noting that "the relationship between the carcinogens and QCA as a marker residue can no longer be considered valid for surveillance purposes."[20] FDA regulations require that there must be a known relationship between the marker residue and the residue of carcinogenic concern. *See* 21 CFR 500.82(b) ("*Marker residue* means the residue … whose concentration is in a known relationship to the concentration of the residue of carcinogenic concern"). Under 21 CFR 500.82(b), "[r]esidue of carcinogenic concern means all compounds in the total residue of a demonstrated carcinogen excluding any compounds judged by FDA not to present a carcinogenic risk." For carbadox, QCA and methyl carbazate have been determined by FDA to be noncarcinogenic. Accordingly, only these compounds can be excluded from the residue of carcinogenic concern.

As CVM explained by letter in 2011, the approved method must "comply with 21 CFR Part 500, Subpart E," which requires "information to establish the appropriate concentration for the marker (R_m)[21] for residues of carcinogenic concern *per* 21 CFR 500.86, and information validating an analytical methodology with a limit of detection at or below the R_m that detects no marker residue in the edible tissue of treated swine at the time of slaughter."[22] CVM further explained the steps required by the regulations during a December 2011 meeting with Phibro:

> 1) submit a definitive total residue study protocol – the objective of the study is to demonstrate when total residues of carcinogenic concern deplete down to the S_m.
>
> 2) submit a proposal for discounting total residues of noncarcinogenic concern.
>
> 3) generate the data to allow a marker residue to total residue of carcinogenic concern ratio and the R_m to be established.
>
> 4) validate method to below R_m (typically 10-20% below proposed R_m).
>
> 5) establish a withdrawal period for carbadox by conducting a residue depletion study[23]

To the extent Phibro was surprised by this approach in 2011, we note that the regulations are clear and therefore provide ample notice of what the law requires. 21 CFR 500.82(b)

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[20] CVM letter dated July 1, 2005, filed in N-041061-G-0117.

[21] R_m means the concentration of the marker residue in the target tissue when the residue of carcinogenic concern is equal to S_m. S_m means the concentration of a residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer. 21 CFR 500.82(b).

[22] Section 512(l) Order (June 15, 2011).

[23] Submission dated December 2, 2011, N-041061-Z-0142, meeting date December 8, 2011, amended MOC N-041061-Y-0143.

("*Residue of carcinogenic concern* means all compounds in the total residue of a demonstrated carcinogen excluding any compounds judged by FDA not to present a carcinogenic risk.").

We acknowledge that CVM's understanding of carbadox metabolism has changed since approving the method in 1998. At that time, CVM concluded that all unidentified residues at 72 hours post-dosing were noncarcinogenic residues related to QCA even though only 25% of the residues had been characterized.[24] Because we now know that a carcinogenic metabolite of carbadox, DCBX, persists more than 72 hours post-dosing, CVM can no longer accept the earlier conclusion that all residues beyond 72 hours are noncarcinogenic. Indeed, Phibro's own expert concluded that DCBX does not deplete to the concentration that represents "no significant increase in risk of cancer to the human consumer" (0.915 ppb) until 23 days post-dosing and is detectable using the CFIA method at 75 days post-dosing. For reasons discussed in our memos concerning the analytical flaws in Phibro's 2008 and 2016 studies,[25] CVM does not accept Phibro's conclusion that no carcinogenic residues are detectable at 42 days post-dosing (the current withdrawal period for carbadox). Furthermore, the assumption that the withdrawal period should remain at 42 days is premature. Before CVM can set a withdrawal period for carbadox, we must know the R_m (i.e., the concentration of the marker residue when the residue of carcinogenic concern depletes to 0.915 ppb). But we do not know when this occurs because, among other things, Phibro did not measure all carbadox residues and then subtract measurements of noncarcinogenic residues in accordance with the definition of residue of carcinogenic concern. 21 CFR 500.82(b).

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[24] After concluding that all carcinogenic residues depleted below detectable levels within 72 hours, CVM approved the supplemental application with a 70-day withdrawal period in January 1998 and later approved a supplemental application that reduced the withdrawal period to 42 days in October 1998. CVM did not reassess the approved method for carbadox during a 2004 supplemental approval for a combination product of carbadox and another animal drug, oxytetracycline. The level of review for combination products is established by section 512(d)(4)(A) of the FD&C Act:

> [T]he Secretary shall not issue an order under paragraph (1)(A), (1)(B), or (1)(D) refusing to approve the application for such combination on human food safety grounds unless the Secretary finds that the application fails to establish that—
>
> (i) none of the active ingredients or drugs intended for use in the combination, respectively, at the longest withdrawal time of any of the active ingredients or drugs in the combination, respectively, exceeds its established tolerance; or
>
> (ii) none of the active ingredients or drugs in the combination interferes with the methods of analysis for another of the active ingredients or drugs in the combination, respectively;

21 U.S.C. 360b(d)(4)(A). For the carbadox and oxytetracycline combination product, CVM confirmed that neither carbadox nor oxytetracycline exceeded its previously established tolerance at the end of the longest withdrawal period and also confirmed that the presence of each drug did not interfere with the method of analysis for the other drug.

[25] Memorandum to File entitled, "CVM Response to Phibro Animal Health Corporation's September 18, 2020 Comments on CVM's July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox" (Jan. 6, 2022); Memorandum to File entitled, "CVM's Review of Documents Phibro Submitted to Docket No. FDA-2021-N-1326 and Phibro's Presentation at the March 10, 2022, Part 15 Public Hearing" (Oct. 30, 2023).

An internal document Phibro submitted to FDA in 2011 entitled (b) (4)

This internal document was at odds with Phibro's statements to CVM. Meetings continued through 2015, and Phibro informed CVM that Phibro anticipated it could submit data to identify an appropriate marker residue and assign a value for the marker residue that corresponded with the 0.915 ppb concentration that represents no significant increase in the risk of cancer to the human consumer. This did not occur.

CVM moved to withdraw the carbadox approvals in 2016. Following review of the sponsor's studies submitted in 2016, CVM decided to address the threshold question of the adequacy of the approved method before withdrawing carbadox under the Delaney Clause. The proposed order in 2020 and public hearing in 2022 again provided opportunities for Phibro to provide the data necessary to identify a method that satisfies the statutory and regulatory requirements. Phibro did not do so, although Phibro maintained that it would be willing to conduct such a study.[26]

CVM believes that the public interest outweighs further delay for the reasons discussed herein and because the available evidence shows that the conclusions CVM relied on in using QCA as a marker residue and setting a withdrawal period of 42 days are not supported by current knowledge of carbadox. To the extent Phibro wishes to present new or additional evidence regarding the adequacy of the approved method or of another

[26] We acknowledge your argument that a stay of the final order "would eliminate the need for emergency proceedings on a motion for temporary restraining order (TRO) or preliminary injunction (PI) regarding the validity of the final order" and would "ensure the efficient use of government resources by eliminating the need for immediate emergency judicial review." Petition at 14. However, our actions are reasonable and lawful for the reasons discussed here, in our response to your petition requesting that FDA "refrain from finalizing, and withdraw, the Proposed Order," Dkt. FDA-2020-P-2312, and in the final order that will be publicly available in the Federal Register. It is an efficient use of government resources to address the adequacy of the approved method before proceeding to an NOOH under the Delaney Clause. Furthermore, it is not clear what purpose "immediate emergency judicial review" would serve when Phibro remains able to market the drug while withdrawal proceedings are ongoing.

method, it may do so in its request for hearing in response to the 2023 NOOH. And, to the extent Phibro still needs to conduct the studies necessary to establish an R_m value and present that data to support an adequate regulatory method for carbadox in the future, it may submit a new application for carbadox with a method that satisfies the regulatory and statutory requirement to show "no residue" in edible tissues.

* * *

Having determined that a stay is not in the public interest and that three of the four factors under 21 CFR 10.35(e) weigh against providing a stay, FDA is denying your request to stay the final order. Accordingly, FDA is denying your stay petition.

Sincerely yours,

William T. Flynn -S Digitally signed by William T. Flynn -S
Date: 2023.11.03 17:13:59 -04'00'

William T. Flynn, DVM, MS
Deputy Center Director
Center for Veterinary Medicine