November 2, 2023

Jeannie Perron, JD, DVM
Covington & Burling LLP
One City Center
850 Tenth Street, NW
Washington, DC 20001-4956

Re: Docket No. FDA-2020-P-2312

Dear Dr. Perron:

This is a final response to the citizen petition (FDA-2020-P-2312) you filed with the Food and Drug Administration (FDA) on November 17, 2020,[1] 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.

In your petition you request that FDA refrain from finalizing, and withdraw, the Proposed Order issued on July 20, 2020, 85 FR 43853, which describes the proposed basis to revoke the approved regulatory method for carbadox. You argue that FDA is required to issue a Notice of Opportunity for Hearing (NOOH) addressing both the method-revocation and proposed NADA withdrawals simultaneously. You argue that this procedure is required under the Federal Food, Drug, and Cosmetic Act (FD&C Act), agency precedent, the Administrative Procedure Act (APA), and the Due Process Clause of the United States Constitution and that this procedure is necessary to provide Phibro with a meaningful opportunity to address its disagreements with CVM on key scientific issues.

After reviewing your arguments, FDA has determined that finalizing the Proposed Order is an appropriate procedure under the FD&C Act, agency precedent, the APA, and the Due Process Clause to resolve uncertainty regarding the approved method for carbadox that measures quinoxaline-2-carboxylic acid (QCA) as a marker residue.[2]

---

[1] On May 18, 2021, FDA tentatively responded to your citizen petition and explained that the agency needed additional time to issue a final response 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] You did not present a substantive defense of the approved method for carbadox in your citizen petition. Nonetheless, CVM notes that the basis for FDA's conclusions regarding the adequacy of the approved method is addressed in the Final Order, which will be publicly available in the Federal Register.

1. *FDA may address whether a regulatory method complies with the regulations by declaratory order when that method has not been adopted by regulation*

Carbadox is one of only a few FDA-approved carcinogenic animal drugs. This is because FDA generally may not approve cancer-inducing animal drugs for food-producing animals. The Delaney Clause in section 512(d)(1)(I) of the FD&C Act, 21 U.S.C. 360b(d)(1)(I), prohibits the approval of carcinogenic new animal drugs unless an exception, known as the "Diethylstilbestrol (DES) Proviso" (DES Proviso), applies. This exception requires a method of examination "prescribed or approved by the Secretary by regulations" for testing residues in any edible portion of treated animals after slaughter or in any food yielded by or derived from the animals. 21 U.S.C. 360b(d)(1)(I). FDA's regulations in 21 CFR part 500, subpart E establish the requirements for satisfying the DES Proviso. The regulations require, among other things, approval of a "regulatory method" to ensure that no residue of a carcinogenic drug will be found in edible portions of animals. 21 CFR 500.88. As a carcinogenic drug used in food-producing animals, carbadox is subject to these statutory and regulatory requirements to ensure no carcinogenic residues remain in edible tissues.[3]

Although FDA approved a regulatory method for carbadox in 1998, this method was not published in the Federal Register, as required by FDA regulations. 21 CFR 500.88(c) ("FDA will publish in the Federal Register the complete regulatory method for ascertaining the marker residue in the target tissue in accordance with the provisions of sections . . . 512(d)(1)(I) . . . of the act."). At the time, FDA concluded that carcinogenic residues depleted within 72 hours post-dosing and approved a regulatory method based on that conclusion, along with other assumptions about depletion of carbadox residues, instead of following the regulatory process for establishing a known relationship between a marker residue and the residue of carcinogenic concern. FDA recognizes that this action was contrary to our regulations and is correcting that mistake by revoking the method based on the regulatory and statutory requirements. *See Cleveland Nat. Air Show, Inc. v. U.S. Dep't of Transp.*, 430 F.3d 757, 765 (6th Cir. 2005) ("A government agency, like a judge, may correct a mistake, and no principle of administrative law consigns the agency to repeating the mistake into perpetuity."). Subsequent information has shown that carbadox residues last longer than previously known, undercutting the assumptions on which the 1998 supplemental approval rested.

The FD&C Act requires that carcinogenic new animal drugs have a regulatory method that comports with the methods of examination prescribed or approved by regulations, but the FD&C Act does not require a specific procedure to determine whether a particular method of examination satisfies the statutory and regulatory requirements, nor does it

[3] In your citizen petition, you state that "carbadox is a potential carcinogen." Petition at 2. As explained further in response to your stay petition, the Delaney Clause applies if an animal drug "induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal." 21 U.S.C. 360b(d)(1)(I). Carbadox was shown to induce cancer in mice and rats in laboratory studies; therefore, the Delaney Clause applies. Carbadox has been regulated as a carcinogenic animal drug since its initial approval in 1972 and has always been treated by the agency and each sponsor as a carcinogen.

address the situation when an agency did not follow a regulatory requirement to publish that method in the *Federal Register*. Given this unusual situation of an approved regulatory method but no rule to amend, FDA issued a declaratory order under 5 U.S.C. 554(e) to remove uncertainty regarding the approved method for carbadox and whether the method satisfies the statutory exemption of the DES Proviso. FDA has used the declaratory order approach before to determine that a drug (and the "me-too" drugs marketed in reliance on the "pioneer" drug application) did not fall under a statutory exemption. *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 626 (1973) (holding that FDA could issue a declaratory order to terminate controversy and remove uncertainty regarding whether a new drug and "me-too" drugs were exempt from providing efficacy data); *see Pfizer Inc. v. Shalala*, 182 F.3d 975, 980 (D.C. Cir. 1999) ("An administrative agency . . . may issue a declaratory order in mere anticipation of a controversy or simply to resolve an uncertainty.").

Issuance of a declaratory order is also consistent with the APA and FDA regulations. The APA defines "order" as "the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rule making but including licensing." 5 U.S.C. 551(6). FDA's regulations state that the Commissioner may initiate a proceeding to issue an order or take any other form of administrative action. 21 CFR 10.25(b); *see also* 21 CFR 10.3(a) (defining "proceeding"). And the regulations, consistent with the APA, define "order" to mean "the final agency disposition, other than the issuance of a regulation, in a proceeding concerning any matter…" 21 CFR 10.3(a). Accordingly, FDA's utilization of a declaratory order to remove uncertainty where there is no rule to amend is appropriate.

2. *Previous withdrawals did not consider whether the approved method was consistent with the regulations*

Since enactment of the DES Proviso in 1962,[4] FDA has withdrawn approvals for carcinogenic new animal drugs under the Delaney Clause on two occasions: first DES (for which the DES Proviso is named) and then drugs in a class of chemicals known as "nitrofurans," including furazolidone, furaltadone, nitrofurazone, and nihydrazone.[5] These withdrawals provide little insight into the appropriate process for revoking the regulatory method for carbadox because they did not address whether the approved method complied with the regulations. It would have been impossible to do so, since, in each instance, the withdrawal proceedings began before FDA published regulations implementing the DES Proviso. FDA did not finalize the regulations for approving

[4] The Delaney Clause was enacted as part of the Food Additives Amendment of 1958. Pub. L. 85-929, 72 Stat. 1784, 1786 (Sept. 6, 1958). At the time, animal drugs used in food-producing animals were regulated as both animal drugs and food additives. The DES Proviso was added to the Delaney Clause in 1962. Pub. L. 87-781, 72 Stat. 780, 785 (Oct. 10, 1962). The Delaney Clause and DES Proviso were moved to their current location by the Animal Drug Amendments of 1968, which consolidated the animal drug and food additive approval requirements for new animal drugs. Pub. L. 90-398, 82 Stat. 342, 345 (July 11, 1968).

[5] FDA earlier withdrew an approval for DES used in chickens beginning in 1959 and concluding in 1965, but this withdrawal relied entirely on the general safety clause. *Bell v. Goddard*, 366 F.2d 177, 179 (7th Cir. 1966).

methods of examination pursuant to the DES Proviso until 1987. 52 FR 49572 (Dec. 31, 1987).[6] These withdrawals also differed from the NOOH that will be publicly available in the Federal Register for carbadox in that they relied on the general safety clause in addition to the Delaney Clause.

FDA's first withdrawal of a carcinogenic drug used in food-producing animals under the Delaney Clause was DES itself, and the initial process was withdrawal first, followed by revocation of the regulations governing the use of DES. FDA initially withdrew the approvals for DES in 1972 (in dry and liquid premixes) and 1973 (in implants) because a newer, more sensitive test used by the U.S. Department of Agriculture (USDA) had detected DES residues in beef livers. *Hess & Clark, Division of Rhodia, Inc. v. Food & Drug Administration*, 495 F.2d 975, 979-81 (D.C. Cir. 1974). However, USDA's method was not the approved regulatory method; the approved method was not sensitive enough to detect the residues. *Id.* at 991. Instead of revoking the previous method and adopting the more sensitive method, FDA published an NOOH that proposed to revoke the DES approvals based on the evidence of carcinogenic residues shown by the USDA results. 37 FR 12251 (June 21, 1972). The Commissioner later concluded that a hearing was unnecessary because there was no process to avoid detectable residues in the edible portions of the animals and withdrew the approvals. 37 FR 15747 (Aug. 4, 1972) (dry and liquid premixes); 38 FR 10485 (Apr. 27, 1973) (implants). Only after withdrawing the approvals did FDA revoke the "use" regulations, which establish the conditions for use in animals, such as withdrawal times, maximum concentrations in feed, and the regulatory method. 37 FR 26307 (Dec. 9, 1972) (dry and liquid premixes); 38 FR 10926 (May 3, 1973) (implants).[7]

Lawsuits followed, and the D.C. Circuit overturned the withdrawals, holding that the NOOH was inadequate because it did not provide the drug sponsors with the USDA test results and a chance to respond to those results. *Hess & Clark*, 495 F.2d at 983; *Chemetron Corp. v. U.S. Dep't of Health, Educ. & Welfare*, 495 F.2d 995, 999 (D.C. Cir. 1974). The court also noted that the Delaney Clause was inapplicable to the withdrawal because the residues had not been detected using the approved method:

> In its regulations, the FDA has approved only the 'mouse uterine' test. Using this test, no residues have been found in the tissues of slaughtered animals. Rather, the only method by which residues have been detected is the radioisotope tracer test, but that method has not been approved. For that reason, the Delaney Clause is plainly inapplicable, without regard to the composition of the residues.

Hess & Clark, 495 F.2d at 991. And the court also stated: "The 'DES' exception to the Delaney Clause … continues effective unless the agency detects residues in a slaughtered

[6] The final rule recounts the history in greater detail. In short, FDA initially proposed regulations in 1973, 38 FR 19226 (July 19, 1973), but had to repropose the regulations for comment several times.

[7] For carbadox, the use regulations are 21 CFR 556.100 and 21 CFR 558.115. CVM will revoke these regulations if the carbadox approvals are withdrawn.

animal while using an approved test method. And the residues detected by the Department of Agriculture were not found by an 'approved method.'" *Chemetron*, 495 F.2d at 999.

Following the court's decisions, FDA proposed rulemaking to revoke the approved methods for measuring DES residues in edible tissue. 39 FR 11299 (Mar. 27, 1974). Two years later, after reviewing comments on the proposed rule, FDA concluded that the approved methods for detecting DES were inadequate and issued an NOOH to revoke the approval of DES on two independent grounds: first, that the drug was no longer shown to be safe for use (the "general safety clause"), and second, that the drug did not satisfy the Delaney Clause because there was no method that was adequate to demonstrate that, within the meaning of the Act, no residues will be found when the drug is used as approved. 41 FR 1804 (Jan. 12, 1976). After an administrative hearing, the agency issued a final rule revoking the approved method. 44 FR 39388 (July 6, 1979). FDA simultaneously withdrew the DES approvals on the basis of the general safety clause and the Delaney Clause. 44 FR 39618 (July 6, 1979); 44 FR 54852 (Sept. 21, 1979) (publishing Commissioner's June 29, 1979 decision). FDA concluded that the Delaney Clause applied in the absence of any approved method. The D.C. Circuit upheld the withdrawal under the general safety clause but declined to address FDA's application of, or procedure regarding, the Delaney Clause. *Rhone-Poulenc, Inc., Hess & Clark Division v. FDA*, 636 F.2d 750, 751-52 & n.2 (D.C. Cir. 1980).

The DES history counsels against withdrawing a carcinogenic animal drug based solely on the Delaney Clause when there is still an approved method that has not identified carcinogenic residue.[8] Unlike in DES, FDA is not here relying on a second basis (e.g., the general safety clause) for the NOOH. The 1974 DES opinions declining to apply the Delaney Clause when there were currently approved methods that did not result in detectable levels of residue suggest that the Delaney Clause will apply only (i) after the approved method has been revoked or (ii) residue is found by the approved method. The process proposed in your citizen petition (addressing both the adequacy of the method and the withdrawal in the same NOOH), *see* Petition at 3, while partially consistent with what FDA did in 1976,[9] on further review appears inconsistent with the only court cases that address the applicability of the Delaney Clause in a withdrawal proceeding when there is still an approved method. Accordingly, CVM chose to first address the adequacy of the approved method for carbadox before relying on the Delaney Clause to take action to withdraw the carbadox approvals.

---

[8] In this instance, the approved method is incapable of identifying carcinogenic residue because it tests for noncarcinogenic QCA and there is no known relationship between QCA and the residue of carcinogenic concern.

[9] Your proposal differs from the 1976 DES proceeding in two ways. In 1974, FDA issued a proposed rule to revoke the method for DES, 39 FR 11299 (Mar. 27, 1974), which the agency finalized after the hearing, 44 FR 39388 (July 6, 1979). FDA also proceeded under both the Delaney Clause and the general safety clause. Your citizen petition does not appear to argue that FDA should issue a proposed rule to revoke the method or proceed under the general safety clause with respect to carbadox.

The withdrawal process for the nitrofurans (furazolidone, furaltadone, nitrofurazone, and nihydrazone) also involved two sets of NOOHs but differed from DES and carbadox because the nitrofurans were not known to be carcinogenic when initially approved, so there was no approved method for the nitrofurans. FDA began the process to withdraw approvals by issuing NOOHs in 1971 that explained that new evidence showed these drugs produced tumors when administered to laboratory animals, raising new safety concerns. 36 FR 5926 (Mar. 31, 1971) (nihydrazone); 36 FR 5927 (Mar. 31, 1971) (nitrofurazone); 36 FR 14343 (Aug. 4, 1971) (furazolidone and furaltadone). FDA did not immediately hold a hearing and continued to work with the sponsors to gather more data. Based on additional information from the drug sponsors and new studies, FDA issued new NOOHs in 1976 concluding that these drugs were carcinogenic and that the methods submitted by the sponsors were insufficiently sensitive to ensure no residue in edible tissues. 41 FR 19907 (May 13, 1976) (furazolidone); 41 FR 34891 (Aug. 17, 1976) (furaltadone); 41 FR 34899 (Aug. 17, 1976) (nitrofurazone); 41 FR 34908 (Aug. 17, 1976) (nihydrazone).

FDA announced in 1977 that it would hold a formal evidentiary hearing for furazolidone, furaltadone, and nitrofurazone because "some previously submitted data, which had not been reviewed before, have been discovered. In addition, some previously reviewed data have been reevaluated in light of contemporary scientific and legal standards for evaluating animal drugs." 42 FR 18660 (Apr. 8, 1977).[10] FDA announced again in 1984 that it would hold a hearing. 49 FR 34965 (Sept. 4, 1984) (nitrofurazone); 49 FR 34967 (Sept. 4, 1984) (furaltadone);[11] 49 FR 34971 (Sept. 4, 1984) (furazolidone). The hearing took place, and the administrative law judge (ALJ) presiding over the hearing found that furazolidone was an animal carcinogen that should be withdrawn under both the Delaney Clause and the general safety clause. 56 FR 41902 (Aug. 23, 1991). He found that nitrofurazone was an animal tumorigen and should be withdrawn under the general safety clause. *Id.* The ALJ found that the sponsors had failed to provide a reliable method of residue detection for either drug. *Id.* In addition, he determined that the concentrations of residues of furazolidone were not shown to be below the level of carcinogenic or toxicological concern. *Id.* After reviewing exceptions to the ALJ's findings asserted by the sponsors, the Commissioner concluded that the evidence in the record supported the ALJ's decision. *Id.* at 41902-03.

The withdrawals for DES and the nitrofurans demonstrate the importance of reviewing all information before proceeding to an NOOH and, when necessary, issuing a new NOOH that identifies the specific grounds for withdrawal. However, the circumstances of these withdrawals differed from carbadox in that DES involved test results from a more sensitive method and the nitrofurans never had an approved regulatory method. None of the withdrawals addressed compliance with regulations implementing the DES Proviso

[10] FDA withdrew the approval for nihydrazone and one NADA for furaltadone in 1977 because no one submitted a request for a hearing for those approvals. 42 FR 17526 (Apr. 1, 1977) (furaltadone); 42 FR 18660 (Apr. 8, 1977) (nihydrazone).

[11] The NADAs for furaltadone that were the subject of this NOOH were withdrawn in 1985 at the sponsor's request. 50 FR 5816 (Feb. 12, 1985).

(which were not final until 1987, after DES had been withdrawn for the second time and after the ALJ held the hearing for furazolidone and nitrofurazone). Furthermore, the court decisions in *Hess & Clark* and *Chemetron* (regarding the first DES drug withdrawals involving the Delaney Clause) highlight the importance of first addressing the adequacy of an approved method before relying on the Delaney Clause. *Hess & Clark*, 495 F.2d at 991; *Chemetron*, 495 F.2d at 999. In issuing a final order revoking the regulatory method for carbadox before proceeding with an NOOH, FDA is following the D.C. Circuit's instructions that the Delaney Clause is "inapplicable" while there is still an approved regulatory method that has not identified carcinogenic residue.

3. *The requirement to issue a notice of opportunity for a hearing applies when FDA proposes to withdraw a new animal drug approval*

Although your citizen petition asserts that a hearing is necessary to revoke an approved method because carcinogenic new animal drugs require an approved method, Petition at 3, an NOOH is required by statute at a specific point in time: when FDA proposes to withdraw a new animal drug approval. Under section 512(e)(1) of the FD&C Act, "the Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application." 21 U.S.C. 360b(e)(1). In keeping with this statutory requirement, FDA will publicly issue an NOOH proposing to withdraw the approvals for carbadox and providing Phibro with an opportunity for a hearing.

Your citizen petition argues that the regulatory method is "inextricably intertwined" with the drug approval such that the two must be addressed in the same NOOH, Petition at 7, but this argument rests on statutory language concerning the scope of a hearing on whether a new animal drug application is approvable in the first instance and an assertion that "the statute is best understood as imposing a parallel requirement that the regulatory method must be evaluated together with a proposal to withdraw approval for a NADA." Petition at 7. The use of language in one section of a statute and not another generally means that Congress intended a difference in meaning. *See Loughrin v. United States*, 573 U.S. 351, 358 (2014). Under section 512(c)(1) of the FD&C Act, FDA must provide the applicant with "notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable" before denying a new animal drug application. 21 U.S.C. 360b(c)(1). By contrast, under the withdrawal process in section 512(e)(1)(B) of the FD&C Act for a drug that has already been approved, FDA "shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application . . . if the Secretary finds . . . that subparagraph (I) of paragraph (1) of subsection (d) [the Delaney Clause] applies to such drug." 21 U.S.C. 360b(e)(1). Here, CVM has made a threshold determination that the DES Proviso does not apply to carbadox and is therefore proceeding with an NOOH under the Delaney Clause. These are two separate issues because "the Delaney Clause is plainly inapplicable" when the approved method does not detect residues. *Hess & Clark*, 495 F.2d at 983. Put differently, while a sponsor may have an opportunity at a hearing held on either NADA approvability under 512(c)(1) or NADA withdrawal under 512(e)(1) to show whether there is an approvable method to meet the DES Proviso, the

FD&C Act does not require an opportunity for a hearing under 512(e)(1) on the interlocutory revocation of an approved method.

Indeed, the statutory provision governing animal drug approvals demonstrates that Congress provides specific language about the timing for an opportunity for a hearing. Under section 512(c)(1) of the FD&C Act, when FDA finds that a ground for denying an application applies, it must "give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) ["Grounds for refusing application"] on the question whether such application is approvable." 21 U.S.C. 360b(c)(1). Because there would be no approved method at that point in time, to the extent the adequacy of a method is contested for a carcinogenic new animal drug, it would necessarily be a subject of a hearing on the drug's approvability. In contrast, with respect to withdrawal, the factual circumstances are different – with an approved carcinogenic new animal drug there would necessarily be an approved method already in place. Nothing in the text of the withdrawal provision of the FD&C Act (21 U.S.C. 360b(e)(1)) requires a hearing on an agency's pre-hearing, interlocutory finding regarding the adequacy of that method. Instead, the statutory withdrawal text provides that the opportunity to request a hearing occurs at a distinct time, i.e., when FDA issues a notice to withdraw the approval. When FDA issues an NOOH proposing to withdraw the carbadox approvals, Phibro can request a hearing by showing a genuine and substantial issue of fact. 21 CFR 514.200(c)(1); *see Nat. Res. Def. Council, Inc. ("NRDC") v. U.S. Food & Drug Admin*., 760 F.3d 151, 172 (2d Cir. 2014) ("We believe, however, that if Congress intended to . . . mandate the commencement of the notice and hearing process whenever the agency staff formed a scientific opinion adverse to the drug, it would have stated those intentions explicitly").

This action is consistent with FDA's long-standing position that determinations on an approved method do not independently require an opportunity for a hearing, but that the opportunity for a hearing applies to the withdrawal itself and can include alternative methods. As explained in the second NOOH for DES:

> The Commissioner notes that the designation of officially approved methodology does not independently require a hearing under the act. However, opportunity for hearing is required on the proposal to withdraw approval of the NADA's for DES, and any hearing held could include the issue of whether a practicable analytical method exists that is adequate to detect DES residues.

41 FR 1804, 1805 (Jan. 12, 1976). The final order, which will be publicly available in the Federal Register, concludes that the approved method that uses QCA as a marker residue is inconsistent with the regulatory and statutory requirements and that insufficient data are available to CVM to replace this method with any known alternative method, such as, but not limited to, the method used by the Canadian Food Inspection Agency to measure desoxycarbadox (DCBX) residues. This determination does not prevent Phibro or any other interested party from providing new or additional data to show that a different analytical method exists that is adequate to detect carbadox residues in accordance with

the statute and regulations or providing new or additional data to support the QCA or DCBX methods.

The revocation of the approved method would not deprive Phibro of a property right without due process, contrary to your assertion in your citizen petition. Petition at 5. As your citizen petition notes, at least one district court has held that a drug sponsor has a constitutionally protected property interest in the "ability to sell its product lawfully in interstate commerce." *Mallinckrodt Inc. v. United States Food & Drug Admin.*, No. CV DKC 14-3607, 2015 WL 13091366, at *16 (D. Md. July 29, 2015); Petition at 5 & n.17. That court explained, however, that this property right was not deprived or impaired when FDA stated that a generic drug was not "therapeutically equivalent" to a brand name drug, even though this change was expected to result in a decrease in market share and financial losses for the generic. *Mallinckrodt*, 2015 WL 13091366, at *16. Because "FDA ha[d] not suspended or revoked [the generic sponsor's] permission to sell its product," the court concluded that the company had not suffered a deprivation of its property right. *Id.*[12] Here, Phibro's interest is in the ability to market carbadox, and that ability remains intact. *See Roberts v. United States*, 741 F.3d 152, 162 (D.C. Cir. 2014) (finding no deprivation of property interest in employment when the plaintiff remained employed).

Although you assert that the final order will result in "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, these types of "consequential injuries" are not constitutionally protected property interests. For example, the D.C. Circuit has held that "consequential injuries" such as loss of stock price or harm to brand value did not merit Due Process Clause protection where they resulted from market reactions to EPA's "unilateral administrative orders (UAOs), directing companies and others to clean up hazardous waste for which they are responsible," rather than from the orders themselves. *Gen. Elec. Co. v. Jackson*, 610 F.3d 110, 113–14 (D.C. Cir. 2010). The D.C. Circuit held that this was the case even though the companies could not directly challenge EPA's unilateral administrative orders in court—their only two options were either to comply and seek reimbursement or refuse to comply and wait for EPA to bring an enforcement action. *Id.* at 115.

Because carbadox can continue to be lawfully marketed unless and until the carbadox NADAs are withdrawn, Phibro has not been deprived of a property interest without due process. The final order addresses an important matter (whether the approved method complies with the statute and its implementing regulations), but it does not deprive Phibro of the ability to sell its product lawfully in interstate commerce. As provided in

[12] With respect to the company's APA claims, the court concluded that the agency had not taken final agency action because it had requested additional data from the drug sponsor but had not made a final decision on the product's therapeutic equivalency or whether the product must be removed from the market. *Mallinckrodt*, 2015 WL 13091366, at *10. The court noted that the requirement for notice and opportunity for a hearing would apply if FDA chose to instigate a withdrawal proceeding. *Id.*; *see NRDC*, 760 F.3d at 168-69 (explaining that decision to issue an NOOH for an animal drug was not a formal finding and "only after the hearing does the final agency action result in formal findings and a resultant order").

the NOOH, Phibro may request a hearing if it believes it can demonstrate there is a genuine and substantial issue of fact that requires a hearing. For instance, it may choose to provide new or additional evidence showing that the QCA method or a different analytical method satisfies the statute and regulations. An alternative method could potentially use QCA, DCBX, or another compound as a marker residue, provided that the concentration of the marker residue is in a known relationship to the concentration of the residue of carcinogenic concern and the data exist to calculate the depletion of the marker residues until the residue of carcinogenic concern is at or below the concentration that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million. 21 CFR 500.82, 500.86. The regulatory method must also be able to confirm the identity of the marker residue in the target tissue at a minimum concentration corresponding to this concentration. 21 CFR 500.88(b). Finally, the "no residue" requirement is met when the marker residue depletes below the limit of detection. 21 CFR 500.82.

4. *The proposed order provided notice and opportunity to comment on the specific issue of revoking the approved method*

FDA issued a proposed order explaining the agency's initial determination that the approved method for carbadox does not satisfy the regulatory and statutory requirements, accepted comments on the order, and reviewed those comments before finalizing the order. FDA also held a public hearing on March 10, 2022, to gather additional data and information related to the residue of carcinogenic concern for carbadox. 87 FR 2093 (Jan. 13, 2022). FDA opened a public docket for the hearing and also considered comments submitted to that docket before finalizing the order. Although notice-and-comment procedures are required for rulemaking, not orders, FDA chose this approach to provide ample opportunity for all interested parties to submit comments. Notably, FDA does not approve regulatory methods through notice-and-comment rulemaking under the APA. *See* 76 FR 72617 (Nov. 25, 2011) (publishing regulatory method to detect residues of carcinogen without notice-and-comment rulemaking). Because notice-and-comment rulemaking is not required to publish a regulatory method, it is not required to revoke a regulatory method. *See Perez v. Mortg. Bankers Ass'n*, 575 U.S. 92, 101 (2015).

Further process is not required under the FD&C Act, APA, or Due Process Clause to revoke an approved method. As explained above, an opportunity to request a hearing is required under the FD&C Act before withdrawing a new animal drug approval, and this opportunity is being provided for carbadox. Under the APA, revoking an approved method falls squarely within the framework of adjudication appropriate for a declaratory order because FDA is determining whether one specific regulatory method complies with the existing regulations that govern all regulatory methods:

> The feature which distinguishes declaratory orders and other interpretative rulings from those legislative rules which must conform with the procedures established by the APA for rulemaking is not the extent of their effect, but rather that the order or ruling instead of creating new law serves only to clarify and state an agency's interpretation of an existing statute or regulation.

Brit. Caledonian Airways, Ltd. v. C. A. B., 584 F.2d 982, 990 (D.C. Cir. 1978). Now that FDA has a general rule on regulatory methods for carcinogenic new animal drugs (which was not the case when FDA issued NOOHs for DES and the nitrofurans), it is appropriate to issue an order determining whether the method for carbadox complies with the regulation. *See Sec. & Exch. Comm'n v. Chenery Corp.*, 332 U.S. 194, 202 (1947) ("Not every principle essential to the effective administration of a statute can or should be cast immediately into the mold of a general rule. Some principles must await their own development, while others must be adjusted to meet particular, unforeseeable situations. In performing its important functions in these respects, therefore, an administrative agency must be equipped to act either by general rule or by individual order. To insist upon one form of action to the exclusion of the other is to exalt form over necessity.").

Although your citizen petition takes issue with the "two-step approach" of revoking the regulatory method first and then issuing an NOOH on the proposal to withdraw the carbadox approvals where there is no approved regulatory method in place, Petition at 8, it is necessary for FDA to determine whether the approved method complies with the regulations before determining if carbadox should be withdrawn under the Delaney Clause. *See Hess & Clark*, 495 F.2d at 991 (noting "the Delaney Clause is plainly inapplicable" when no residues were found in tissues of slaughtered animals using the approved method even though a more sensitive method detected residues); *Chemetron*, 495 F.2d at 999. When an agency action depends on an initial finding, it is appropriate for the agency to address the threshold finding first. *See CSX Transp., Inc. v. Surface Transp. Bd.*, 774 F.3d 25, 27 (D.C. Cir. 2014) (explaining that Surface Transportation Board has the power to review and modify railway rates only if it determines that the railroad has "market dominance" over the transportation route to which the rate applies).[13]

Finally, FDA has provided you notice of the proposed action and "a meaningful opportunity to present [your] case," which is the very essence of what due process requires. *Mathews v. Eldridge*, 424 U.S. 319, 348–349 (1976). A meaningful opportunity to be heard can usually be accomplished with something less than a full evidentiary hearing. *Id.* at 343. The level of formality depends on the importance of the interests involved and the nature of the subsequent proceedings. *Cleveland Bd. of Educ. v.*

---

[13] Your citizen petition cites *James Madison Ltd. Ex. Rel. Hecht v. Ludwig*, 82 F.3d 1085 (D.C. Cir. 1996), to support the assertion that under the APA, parties to an adjudication are "entitled to a hearing before a neutral decision-maker." *Id.* at 1099; Petition at 5-6 & n.20. This case actually involves a Due Process claim and is about the appropriate timing of a hearing, so we consider it alongside your due process arguments. In *Ludwig*, the Comptroller of the Currency declared two banks insolvent and appointed the Federal Deposit Insurance Corporation (FDIC) receiver of both institutions. *Id.* at 1090. Although the banks argued they were entitled to an administrative hearing by an impartial officer before the seizure or, at the very least, before FDIC's liquidation of the banks' assets, the D.C. Circuit concluded that post-deprivation judicial proceedings satisfied due process in light of the public interest in protecting the stability and integrity of the banking system and the procedural safeguards that provided the banks ample notice and many opportunities to express their views. *Id.* at 1099-1100. Here, before carbadox can be removed from the market, Phibro is entitled under the FD&C Act to an opportunity to request a hearing. The timing of this opportunity is, in fact, far earlier than what the banks received in *Ludwig* because it occurs before the carbadox approvals can be withdrawn.

Loudermill, 470 U.S. 532, 545 (1985) (noting that Supreme Court has only once required a full adversarial evidentiary hearing prior to adverse governmental action). In *Loudermill*, the Supreme Court held that an opportunity to present reasons "either in person or in writing" was sufficient for a pre-termination hearing because a fired employee was later entitled to a full administrative hearing and judicial review under state law. *Id.* at 545-57.

Due process requirements are "flexible and call[] for such procedural protections as the particular situation demands." *Mathews*, 424 U.S. at 334. Under the three-part *Mathews* test, courts weigh (1) "the private interest… affected by the official action," and (2) "the risk of an erroneous deprivation of such interest through procedures used, and the probable value, if any, of additional or substitute procedural safeguards"; against (3) "the Government's interest, including… the fiscal and administrative burdens" of additional or substitute procedural requirements. *Id.* at 335. Here, CVM's approach satisfies due process given the minimal private interest, robust procedural safeguards, and strong government interest in resolving threshold matters at the outset.

Phibro's private interest in the regulatory method is its continued ability to market carbadox, but this interest is not as weighty because Phibro remains able to sell carbadox. Even assuming revocation of the method will ultimately result in withdrawal of the three carbadox approvals, this financial interest would be considered in the context of Phibro's entire drug portfolio. *See Wilmina Shipping AS v. United States Dep't of Homeland Sec*., 934 F. Supp. 2d 1, 18 (D.D.C. 2013) (concluding that plaintiff's interest in maintaining a certificate required for its ship to operate in U.S. waters was not significant because "deprivation of the certificate does not prevent the [plaintiff] from calling on ports outside U.S. waters, nor does it prevent any other ships plaintiffs may have from calling on ports in the United States"). Phibro remains able to sell carbadox unless the drug is withdrawn; it can also continue to sell other approved animal drugs and can sell carbadox in the countries where it is legal. Carbadox is also a small portion of Phibro's overall sales: Phibro reported Mecadox (carbadox) sales of $20 million for the 12 months ending June 30, 2023, which is about 2% of its total of $978 million net sales for that fiscal year.[14]

There is little risk of an erroneous deprivation through the declaratory order procedure used by FDA because a withdrawal does not occur until there has been an opportunity to request a hearing and, on the specific matter of the adequacy of the approved method, FDA has provided Phibro and other stakeholders with a thorough explanation of FDA's conclusions and multiple opportunities to present data and counter arguments, including from Phibro's own experts and in response to opinions by CVM's experts and including an opportunity for an oral presentation. These are the types of scientific data and reports that are particularly well suited to review on a paper record. *Mathews*, 424 U.S. at 345 ("The conclusions of physicians often are supported by X-rays and the results of clinical

[14] 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.

or laboratory tests, information typically more amenable to written than to oral presentation."). There is professional disagreement on the scientific matters involved, but the "specter of questionable credibility and veracity is not present." *Id.* at 344 (quoting *Richardson v. Perales*, 402 U.S. 389, 407 (1971)).

The alternative procedure you propose is a full evidentiary hearing with "an impartial adjudicator such as the FDA Commissioner, his/her delegate, or an administrative law judge." Petition at 8. Bias sufficient to violate due process is shown by "the kind of personal or financial stake in the decision that might create a conflict of interest" or evidence "in the record to support charges of personal animosity." *Hortonville Joint Sch. Dist. No. 1 v. Hortonville Educ. Ass'n*, 426 U.S. 482, 492 (1976). Your citizen petition does not assert any such bias, nor are we aware of any. CVM is the component of FDA charged with applying the Delaney Clause and DES Proviso and is well-suited to "applying [our] agency's regulation to complex or changing circumstances." *Martin v. Occupational Safety & Health Rev. Comm'n*, 499 U.S. 144, 151-52 (1991). Although CVM has been involved in the events preceding the final order (as expected of an agency carrying out its statutory duties), prior involvement in an ongoing matter does not infect a decisionmaker with bias. *See Hortonville*, 426 U.S. at 496 (holding that school board's involvement in events preceding its decision to terminate schoolteachers did not prevent the school board from serving as impartial decisionmakers).

It is generally the case that something less than a full evidentiary hearing satisfies the requirements of due process, *Arriva Med. LLC v. United States Dep't of Health & Hum. Servs*., 239 F. Supp. 3d 266, 285 (D.D.C. 2017), and this situation differs significantly from the potentially grievous loss of welfare benefits that required an adverse evidentiary hearing in *Goldberg v. Kelly*, 397 U.S. 254, 263 (1970). In *Goldberg*, the Supreme Court held that a welfare recipient at risk of losing life-sustaining benefits "must be allowed to state his position orally" because "[w]ritten submissions are an unrealistic option for most recipients, who lack the educational attainment necessary to write effectively and who cannot obtain professional assistance." *Id.* at 269. Those circumstances are not present here, where Phibro had an opportunity to present orally and in writing with the assistance of counsel and expert witnesses with advanced degrees. This opportunity is fully in keeping with the requirements of due process. *See Mathews*, 424 U.S. at 348 ("The judicial model of an evidentiary hearing is neither a required, nor even the most effective, method of decisionmaking in all circumstances."); *L.B. Wilson, Inc. v. F.C.C.*, 170 F.2d 793, 805 (D.C. Cir. 1948) ("[A] hearing in its very essence demands that he who is entitled to it shall have the right to support his allegations by argument however brief, and, if need be, by proof, however informal.").

In addressing first the revocation of the regulatory method and second the withdrawal of the carbadox approvals, FDA is providing an opportunity to be heard "at a meaningful time and in a meaningful manner," *Mathews*, 424 U.S. at 333, even if these opportunities do not occur at the same time for both matters. Due process does not require all process to occur at the same time. For example, the Supreme Court endorsed a stepwise approach in *Mathews*, holding that there was sufficient process before terminating disability benefits because the agency provided "a summary of the evidence that it considers most

relevant" as well as an opportunity "to submit additional evidence or arguments, enabling [the recipient] to challenge directly the accuracy of information in his file as well as the correctness of the agency's tentative conclusions." *Id.* at 346. The recipient then had a right to an evidentiary hearing, as well as to subsequent judicial review, before the denial of his claim became final. *Id.* at 349. Here, unlike the plaintiff in *Mathews* who could not retain his social security benefits once terminated but prior to further administrative review, Phibro retains its ability to market carbadox until the withdrawal process is complete.

Additional procedures would add little value because there is already a significant safeguard in the form of the opportunity to request a hearing prior to withdrawal, as well as judicial review after final agency action. *CSX Transp., Inc. v. Surface Transp. Bd*., 774 F.3d 25, 33 (D.C. Cir. 2014) ("If an agency interprets the law in an adjudication, a party can challenge that interpretation as being inconsistent with the agency's organic statute, or with its regulations.").

FDA's interest is ensuring that the approved method complies with the applicable regulations and thereby fulfills our statutory mandate to guarantee there is a suitable method prescribed by regulation to show that no residue of carcinogenic new animal drugs remains in edible tissues. The law draws a clear distinction between cancer-inducing drugs and all other hazards: "For all safety hazards other than carcinogens, Congress made safety the issue, and authorized the agency to pursue a multifaceted inquiry in arriving at an evaluation. For carcinogens, however, it framed the issue in the simple form," thereby requiring the agency to deny a listing for a carcinogenic color additive without allowing for a *de minimis* exception. *Pub. Citizen v. Young*, 831 F.2d 1108, 1112 (D.C. Cir. 1987).[15] In keeping with the rigid statutory text, "FDA need not await demonstration of a danger to public health before enforcing the act's requirements that . . . any cancer-causing drug be demonstrated to leave no detectable residues." 41 FR 1804, 1806 (Jan. 12, 1976). Moreover, addressing the threshold question of the existing method's compliance with the regulations before delving into the possible other methods that might be considered during the withdrawal process serves administrative efficiency. Based on all the evidence currently before the agency, providing a full evidentiary hearing on whether the approved method for carbadox complies with the regulations would impose a significant administration burden and would frustrate the agency's congressionally imposed mandate to ensure that no residues of carcinogenic new animal drugs remain in edible tissues. "[T]he Government's interest, and hence that of the public, in conserving scarce fiscal and administrative resources is a factor that must be weighed," *Mathews*, 424 U.S. at 348, and here weighs strongly in favor of the two-step process.

For these reasons, FDA is rejecting your argument that publishing a final order revoking the approved method and then issuing an NOOH on FDA's proposal to withdraw the

[15] This case involved a color additive. 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).

carbadox approvals does not provide Phibro with a meaningful opportunity to address disagreements on key scientific issues related to the proposed order. Phibro has had multiple opportunities to provide relevant arguments and data and will be afforded an opportunity to present new or additional data in its request for a hearing. These opportunities and FDA's process comport with the FD&C Act, agency precedent, the APA, and the Due Process Clause. Accordingly, FDA is denying your citizen petition.

Sincerely yours,

William T. Flynn -S Digitally signed by William T. Flynn -S
Date: 2023.11.02 09:06:16 -04'00'

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