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Petition for Stay of Action Pursuant to 21 C.F.R. § 10.35
Docket No. FDA-2020-N-0955

The undersigned submits this combined Citizen Petition and Petition for Stay on behalf of Phibro Animal Health Corporation, owner of the New Animal Drug Applications (NADAs) for carbadox, a safe and effective antimicrobial drug that has been used to treat pigs for 48 years.

On July 20, 2020, the Center for Veterinary Medicine (CVM) published a proposed declaratory order (Proposed Order) that, if adopted, would revoke the regulatory method for carbadox and set in motion a new proceeding to withdraw marketing approval for carbadox altogether. That two-step approach is unprecedented: In *every* prior case involving application of Section 512(d)(1)(I) of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 360b(d)(1)(I)) to an approved animal drug, FDA has considered the validity of the regulatory method and withdrawal of the NADA approval together in a single, comprehensive proceeding before an impartial adjudicator. The process CVM has proposed here, in contrast, would split those issues into two separate proceedings, the first of which would occur before CVM alone. In Phibro's view, CVM's unprecedented approach is contrary to the governing statute, longstanding agency precedent, and the Administrative Procedure Act (APA).

Phibro submits this petition with the aim of providing an orderly means for resolving the issues raised in the Proposed Order and Phibro's comments in opposition, filed on September 18, 2020. Specifically, Phibro requests in this petition that FDA refrain from finalizing, and withdraw, the Proposed Order, thereby allowing for a new, comprehensive Notice of Opportunity for Hearing (NOOH) proceeding addressing the method-revocation and NADA approval issues together, just as FDA has done in the past. In the alternative, Phibro requests that the

Commissioner of Food and Drugs 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.

There is no health- or safety-related reason not to grant the relief requested in this petition. The Proposed Order does not challenge the safety of carbadox, and a contemporaneously issued CVM notice does not recommend that consumers make dietary changes relating to carbadox. Indeed, although carbadox is a potential carcinogen, FDA has repeatedly concluded that it is safe and effective when used as labeled, including when FDA approved carbadox in 1972, and when it approved supplemental or additional original carbadox applications in 1975, 1998, and 2004. In its 48 years of use, there is not a single known case of carbadox causing cancer in swine or humans. Despite these facts, the Proposed Order seeks to initiate the process of taking carbadox off the market based on (1) a procedural concern that the agency failed to follow its own regulations in 1998 when prescribing the current regulatory method and (2) data that, in CVM's view, calls into question whether the regulatory method uses an appropriate marker residue. Those issues are undoubtedly important and deserve careful attention. However, they can and should be adjudicated in an orderly fashion that adheres to governing law, provides Phibro with a meaningful opportunity to address its disagreements with CVM on key scientific issues, and avoids unnecessary interim marketplace uncertainty regarding the regulatory status of carbadox. Granting the relief requested would address all of those concerns.

I. Decision Involved

CVM published the Proposed Order on July 20, 2020.[1] The Proposed Order would, if finalized, revoke the approved carbadox regulatory method on two interrelated grounds. *First*, the Proposed Order asserts that CVM approved the current carbadox regulatory method in 1998 without requiring that the method "compl[y] with [21 C.F.R.] § 500.88"—for example because the approved method relies on a tolerance level rather than a R_m value as defined in 21 C.F.R. § 500.86.[2] *Second*, the Proposed Order contends that the approved method is "inadequate to monitor residue of carcinogenic concern in compliance with FDA's operational definition of no residue because there is no established relationship between [quinoxaline-2-carboxylic acid] measured by the approved method and the residue of carcinogenic concern."[3]

CVM has stated that if it finalizes the Proposed Order, CVM then "intend[s] to publish" a NOOH "proposing to withdraw approval of all new animal drug applications for use of carbadox

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[1] *See* FDA, *Phibro Animal Health Corp.: Carbadox in Medicated Swine Feed; Revocation of Approved Method*, 85 Fed. Reg. 43,853 (July 20, 2020) (Proposed Order). The Proposed Order is the latest in a series of CVM actions concerning carbadox. For an overview of the relevant history, see *Phibro Animal Health Corporation's Comments on CVM's July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox*, Docket No. FDA-2020-N-0955, at 15–34 (Sept. 18, 2020), *available at* https://www.regulations.gov/docket?D=FDA-2020-N-0955 (Phibro Comments).

[2] 85 Fed. Reg. at 43,854–55.

[3] *Id.* at 43,853.

based on the lack of an approved [regulatory] method," "as required by … section 512(d)(1)(I) of the FD&C Act."[4]

The comment period for the Proposed Order closed on September 18, 2020. Phibro submitted timely comments opposing the Proposed Order. Phibro's comments explain that (1) the Proposed Order would unlawfully deprive Phibro of a meaningful hearing before an impartial adjudicator and conflicts with both agency precedent and the APA; (2) the approved regulatory method remains appropriate, and a well-established alternative method is available; (3) CVM's proposed approach is inequitable; and (4) removing carbadox from the market would have serious health and economic consequences.[5] If FDA finalizes the Proposed Order prior to initiating a new NADA withdrawal proceeding (without first staying the Proposed Order's effect), Phibro intends to challenge revocation of the carbadox regulatory method in federal court.

II. Action Requested

Pursuant to FDA's regulations at 21 C.F.R. § 10.30, the undersigned requests that FDA refrain from finalizing, and withdraw, the Proposed Order to revoke the approved carbadox regulatory method. In the alternative, the undersigned requests pursuant to 21 C.F.R. § 10.35 that the Commissioner immediately stay the effective date of any final order revoking the approved carbadox regulatory method, pending final resolution of any new NADA withdrawal proceeding relating to carbadox.

III. Statement of Grounds

A. FDA should not finalize CVM's unlawful Proposed Order.

Phibro respectfully requests, pursuant to 21 C.F.R. § 10.30, that FDA refrain from finalizing, and withdraw, the Proposed Order. That order would, if finalized, violate Phibro's statutory, regulatory, and constitutional rights. The FDCA and FDA's regulations entitle Phibro to a hearing before approval of the carbadox NADAs is withdrawn, and that hearing must occur before an impartial adjudicator. Because the validity of the regulatory method is inextricably intertwined with approval of the NADAs, Phibro is likewise entitled to a hearing on issues related to revocation of the regulatory method. CVM's proposed two-step process would contravene longstanding agency precedent and bedrock APA requirements by denying Phibro that hearing on the method. Similarly, the narrow NADA withdrawal proceeding contemplated in the Proposed Order would deprive Phibro of its right to defend the carbadox regulatory method before an impartial adjudicator. Accordingly, the Proposed Order should be withdrawn, and, consistent with past agency practice, CVM should adjudicate its concerns regarding the regulatory method in a new, comprehensive NADA withdrawal proceeding.

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[4] *Id.* at 43,854.

[5] *See* Phibro Comments at 34–92.

1. CVM lacks authority to revoke the carbadox regulatory method in a standalone proceeding.

The FDCA generally prohibits approval of animal drugs that "induc[e] cancer when ingested by man or animal"—a provision known as the Delaney Clause.[6] An exception in that provision—known as the diethylstilbestrol (DES) Proviso—states that the Delaney Clause "shall not apply" if FDA determines that the drug (1) "will not adversely affect the animals for which it is intended" and (2) "no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations ...), in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals."[7] FDA approved carbadox pursuant to the DES Proviso in 1972 and has reaffirmed its approval of carbadox on several subsequent occasions, most recently in 2004.[8]

The FDCA authorizes FDA to withdraw NADA approvals, but only after first providing the NADA owner notice and opportunity for a hearing.[9] The statutory criteria for withdrawal include a finding that "new evidence" or "tests by new methods" show that the Delaney Clause applies—for example because the DES Proviso is no longer met.[10] As noted above, the Proposed Order indicates that CVM is planning to rely on this language in a future NADA withdrawal proceeding "based on the lack of an approved [regulatory] method for" carbadox.[11]

If CVM seeks to withdraw an approved NADA on any basis, including that there is no longer an approved regulatory method as required by the DES Proviso, FDA's regulations entitle the sponsor to a formal evidentiary hearing in front the FDA Commissioner, a delegated member

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[6] FDCA § 512(d)(1)(I) (21 U.S.C. § 360b(d)(1)(I)).

[7] *Id.* FDA's implementing regulations refer to "methods of examination prescribed or approved by the Secretary" as "regulatory methods." *See* 21 C.F.R. § 500.80(a) ("The [FDCA] prohibits the use in food-producing animals of any compound found to induce cancer when ingested by people or animals unless it can be determined by methods of examination prescribed or approved by the Secretary (a function delegated to the Commissioner of Food and Drugs) that no residue of that compound will be found in the food produced from those animals under conditions of use reasonably certain to be followed in practice. This subpart identifies the steps a sponsor of a compound shall follow to secure the approval of the compound."); 21 C.F.R. § 500.82(b) ("*Regulatory method* means the aggregate of all experimental procedures for measuring and confirming the presence of the marker residue of the sponsored compound in the target tissue of the target animal.").

[8] *See* FDA, *Tolerances for Residues of New Animal Drugs in Food; Carbadox*, 37 Fed. Reg. 20,683–85 (Oct. 3, 1972); 40 Fed. Reg. 45,164–65 (Oct. 1, 1975); 63 Fed. Reg. 13,337 (Mar. 19, 1998); 63 Fed. Reg. 59,216, 59,216 (Nov. 3, 1998); 69 Fed. Reg. 51,173, 51,173 (Aug. 18, 2004).

[9] FDCA § 512(e)(1) (21 U.S.C. § 360b(e)(1)).

[10] FDCA § 512(e)(1)(B) (21 U.S.C. § 360b(e)(1)(B)) ("The Secretary shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application ... if the Secretary finds— ... subparagraph (I) of paragraph (1) of subsection (d) applies to such drug.").

[11] 85 Fed. Reg. at 43,854.

of the Commissioner's office, or an administrative law judge.[12] The hearing must include an opportunity for the sponsor to present testimony, including oral testimony, and an opportunity to cross-examine adverse witnesses.[13] FDA's regulations also entitle the sponsor to an impartial adjudicator, and FDA establishes a strict separation between the investigative and adjudicative functions during a formal evidentiary hearing.[14] This arrangement ensures that CVM, the center seeking to withdraw the NADA approval, is not also the decision maker regarding issues raised at the hearing.[15]

In addition, the Fifth Amendment's Due Process Clause and the APA require FDA to provide notice and an opportunity to be heard by an impartial adjudicator before withdrawing a NADA.[16] When FDA approves a NADA, it grants the sponsor permission to market the drug lawfully in interstate commerce. This authorization constitutes a significant property right that cannot be revoked without due process.[17] In this context, due process requires that FDA provide the sponsor an evidentiary hearing before "an 'impartial and disinterested' adjudicator,"[18] and the hearing must provide the sponsor a "meaningful" opportunity to contest the proposed withdrawal.[19] Similarly, under the APA, parties to agency adjudication are "entitled to a hearing

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[12] 21 C.F.R. § 514.201 ("Hearings relating to new animal drugs under section 512(d) and (e) of the act shall be governed by part 12 of this chapter."); 21 C.F.R. § 12.60.

[13] 21 C.F.R. § 12.87(b)(1)(i) ("If the proceeding involves particular issues, each party may determine whether, and the extent to which, each wishes to present direct testimony orally or in writing."); *id.* § 12.87(b)(1)(ii) ("Oral cross-examination of witnesses will be permitted if it appears that alternative means of developing the evidence are insufficient for a full and true disclosure of the facts and that the party requesting oral cross-examination will be prejudiced by denial of the request or that oral cross-examination is the most effective means to clarify the matters at issue.").

[14] 21 C.F.R. § 10.55(b)(2)(i).

[15] FDA has explained that "this separation of functions 'reflects FDA's understanding that throughout the withdrawal process, CVM does not speak on behalf of' the FDA." *Nat. Res. Def. Council, Inc. v. FDA*, 760 F.3d 151, 165 (2d. Cir. 2014).

[16] *Mathews v. Eldridge*, 424 U.S. 319, 332 (1976) ("Procedural due process imposes constraints on governmental decisions which deprive individuals of 'liberty' or 'property' interests within the meaning of the Due Process Clause of the Fifth or Fourteenth Amendment.").

[17] *Mallinckrodt Inc. v. FDA*, No. CV DKC 14-3607, 2015 WL 13091366, at *16 (D. Md. Jul. 29, 2015) (drug sponsor had protected property interest in FDA drug approval).

[18] *See, e.g., Cleveland Bd. of Educ. v. Loudermill*, 470 U.S. 532, 542 (1985); *Delaware Riverkeeper Network v. FERC*, 895 F.3d 102, 111 (D.C. Cir. 2018), *abrogated in part on other grounds, Allegheny Def. Project v. FERC*, 964 F.3d 1 (D.C. Cir. 2020); *Hudson v. AFGE*, 292 F. Supp. 3d 145, 154 (D.D.C. 2017) ("The right to an impartial tribunal is one of the most fundamental aspects of due process."); *Am. Chiropractic Ass'n v. Shalala*, 108 F. Supp. 2d 1, 9 n.7 (D.D.C. 2000) ("[B]ias during any ... administrative proceedings will constitute an appropriate ground for reversing the agency's determination").

[19] *Mathews*, 424 U.S. at 333 ("The fundamental requirement of due process is the opportunity to be heard 'at a meaningful time and in a meaningful manner.'" (cleaned up)); *L.B. Wilson, Inc. v. FCC*, 170 F.2d 793, 805 (D.C. Cir. 1948) ("Due process requires not only opportunity for the presentation of evidence and cross-examination of witnesses but also opportunity for argument.").

before a neutral decision-maker."[20] The statutory and regulatory provisions regarding NADA withdrawal proceedings must be interpreted with these bedrock procedural requirements in mind.

"The only bases for permitting withdrawal of approval for an NADA without a prior hearing are (1) the statutory proviso relating to emergency action in the face of an imminent hazard to health, and (2) the provisions in the regulations for 'summary judgment.'"[21] Neither exception applies here. CVM has not asserted that carbadox poses an imminent hazard to health. In fact, CVM recently took the opposite approach by withdrawing a 2016 NOOH that sought to remove carbadox from the market on safety grounds,[22] and by publishing a Frequently Asked Questions document indicating that consumers need not make dietary changes as a result of the Proposed Order.[23] FDA's summary judgment regulations require the agency to grant a hearing if there is any "genuine and substantial issue of fact [that] precludes" withdrawal of the application,[24] and in this case, many such questions remain unresolved. Among other things, the disagreement between Phibro and CVM regarding the adequacy of the approved carbadox regulatory method raises a genuine and substantial issue of fact that justifies a hearing. Phibro and CVM also disagreed on several key scientific issues in the course of the 2016 NOOH proceeding, and CVM acknowledged in an April 17, 2017 letter that a hearing is warranted with respect to those issues as well.[25]

2. *The regulatory method is inextricably intertwined with the NADA withdrawal proceeding that CVM proposes to undertake.*

Questions regarding adequacy of the approved carbadox regulatory method cannot be severed from the NADA withdrawal proceeding because the method is at the heart of CVM's proposed basis for withdrawing the NADA approvals. The basis for CVM's anticipated NADA withdrawal proceeding—evidence that the DES Proviso is not met—turns exclusively on the adequacy of the regulatory method. The original sponsor of the carbadox NADAs submitted a regulatory method for evaluation, and FDA approved the NADA that relied on that regulatory

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[20] *James Madison Ltd. ex. rel. Hecht v. Ludwig*, 82 F.3d 1085, 1099 (D.C. Cir. 1996).

[21] *Hess & Clark, Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975, 982 (D.C. Cir. 1974); *see also* FDCA § 512(e)(1) (21 U.S.C. § 360b(e)(1)) (permitting the Secretary to immediately "suspend the approval" of a NADA upon finding "that there is an imminent hazard to the health of man or of the animals for which [the] drug is intended"); 21 C.F.R. § 514.200(c)(2) (summary judgment regulation).

[22] *See* 85 Fed. Reg. at 43,852.

[23] *See* FDA, *Questions and Answers regarding Carbadox* (July 17, 2020), https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox (FDA "is not recommending that people make changes in their food choices" in response to CVM's proposal to revoke the approved regulatory method for carbadox).

[24] 21 C.F.R. § 514.200(c)(2).

[25] *See* Phibro Comments at 30–32 (citing Docket No. FDA-2016-N-0832, Doc. No. 0052, Center for Veterinary Medicine's Recommendation to Grant, in Part, Phibro Animal Health Corporation's Request for Hearing, at 10–13 (Apr. 17, 2017)).

method to show that the DES Proviso was met.[26] CVM now proposes to revoke the approved method for carbadox, without first holding an evidentiary hearing, based on its unproven allegation that the method is inadequate—and then to initiate a new NADA withdrawal proceeding premised on that action (also apparently without holding an evidentiary hearing). The adequacy of the approved carbadox regulatory method is thus CVM's *sole* basis for seeking to withdraw the NADA approvals, such that the two issues are inextricably intertwined and must be considered together in a hearing.[27]

The statutory provision governing NADA approvals reinforces the necessity for a hearing to resolve disputes about the adequacy of a regulatory method. After a NADA is submitted, FDA must "either (A) issue an order approving the application . . . or (B) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable."[28] Subsection (d) addresses questions central to approvability, including whether the drug should not be approved because the drug "induces cancer when ingested by man or animal," or whether the drug can be approved in spite of its carcinogenic properties because FDA has approved a regulatory method under the DES Proviso.[29]

Therefore, the statute specifically identifies the applicability of the DES Proviso as a basis for a hearing. FDA must refuse to approve a NADA if FDA finds that the drug is a carcinogen "after due notice to the applicant . . . and giving him an opportunity for a hearing."[30] But "[i]f, after such notice and opportunity for hearings," FDA finds that, among other things, the DES Proviso is satisfied, FDA is directed to "issue an order approving the application."[31] As these provisions illustrate, the adequacy of a regulatory method is intertwined with the question whether a NADA may be approved. If an applicant is entitled to a hearing on the front end as to whether a regulatory method is adequate to ensure applicability of the DES Proviso, then that same basic level of process must also apply on the back end to a sponsor seeking to defend the regulatory method of an already-approved drug. Because the adequacy of a regulatory method must be considered in the course of approving a NADA implicating the DES Proviso, and may be decided only *after* conducting a hearing if approvability is in question, 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.[32]

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[26] *See* 37 Fed. Reg. at 20,683.

[27] Although the Proposed Order does not invoke the General Safety Clause in section 512(e)(1) of the FDCA (21 U.S.C. § 360b(e)(1)), the same analysis would apply if FDA had invoked that provision (as it did in the 2016 NOOH). *See* FDA, *Phibro Animal Health Corp.: Carbadox in Medicated Swine Feed; Opportunity for Hearing*, 81 Fed. Reg. 21,559, 21,564–65 (Apr. 12, 2016).

[28] FDCA § 512(c)(1) (21 U.S.C. § 360b(c)(1)).

[29] FDCA § 512(d)(1)(I) (21 U.S.C. § 360b(d)(1)(I)).

[30] FDCA § 512(d)(1) (21 U.S.C. § 360b(d)(1)).

[31] FDCA § 512(d)(1) (21 U.S.C. § 360b(d)(1)).

[32] *See FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000) (statutes must be interpreted "as a symmetrical and coherent regulatory scheme," in which "all parts" "fit, if possible, . . . into an harmonious whole") (citations omitted).

3. CVM's proposed bifurcated approach would violate Phibro's statutory, regulatory, and constitutional rights.

The two-step approach described in the Proposed Order is unlawful because it would deprive Phibro of a meaningful hearing on the adequacy of the approved carbadox regulatory method. Phibro and CVM disagree regarding whether the regulatory method is adequate and whether the DES Proviso is satisfied. To resolve that dispute, Phibro is entitled to a hearing before an impartial adjudicator, in which Phibro can (1) present expert testimony regarding why the regulatory method is scientifically sound and (2) question CVM's experts about their analysis, interpretation of the science, and the basis for their conclusion that the regulatory method should be revoked.

Despite that requirement, CVM is seeking to resolve questions regarding the adequacy of the approved carbadox regulatory method without holding an evidentiary hearing, and without involving an impartial adjudicator. Instead, the Proposed Order indicates that CVM—the FDA branch that has concluded the regulatory method is inadequate and is proposing to revoke the regulatory method—would serve as the decision maker on these questions.[33] That approach, in which CVM would serve as proponent and adjudicator all at once, conflicts with the constitutional, statutory, and regulatory requirements discussed above. It also conflicts with FDA's well-established procedure for conducting NADA withdrawal proceedings in which CVM institutes the proceeding by publishing a NOOH, but does not serve as the decision maker—a role carried out instead by an impartial adjudicator such as the FDA Commissioner, his/her delegate, or an administrative law judge.[34]

FDA cannot cure this violation of Phibro's rights by granting a hearing in a NADA withdrawal proceeding *after* it has finalized an order revoking the regulatory method. The Proposed Order contemplates a new NADA withdrawal proceeding solely on the basis of the lack of a regulatory method. That hearing would occur *after* CVM had revoked the method and thus resolved, without affording to Phibro the impartial adjudication to which it is entitled, a central material issue in the NADA withdrawal proceeding. Such a hearing would not comport with due process or FDA's statutory and regulatory obligations because Phibro would already have been stripped of one of the key bases for requesting a hearing—the adequacy of the current method.

FDA should not finalize the Proposed Order, because doing so would defeat the purpose of the statutory hearing requirement by stripping the administrative hearing of one of its primary functions. Thus, the Proposed Order violates the rule that agencies must interpret statutes in a way that advances, rather than frustrates, their core purposes and overall design.[35] Rescinding

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[33] *See, e.g.*, 85 Fed. Reg. at 43,858 ("New information available to CVM since the approval of the January 1998 supplemental NADA reinforces the importance of having an approved regulatory method that complies with the SOM regulations. Therefore, we are proposing to revoke the current approved method.").

[34] *See* 21 C.F.R. § 12.60.

[35] *See, e.g.*, *King v. Burwell*, 576 U.S. 473, 492–93 (2015) (declining to interpret statute in a manner that would "negate [its] own stated purposes") (citation omitted).

the Proposed Order—and instead allowing CVM to proceed with a new, comprehensive NADA withdrawal proceeding—would address these problems.

4. FDA precedent requires the validity of the regulatory method to be considered as part of a NADA withdrawal proceeding.

FDA should also refrain from finalizing the Proposed Order because doing so would be inconsistent with FDA precedent, and therefore arbitrary and capricious. Agency action is arbitrary and capricious if the agency departs from its own precedent without (1) acknowledging the departure and (2) providing a reasoned justification for doing so.[36]

The Proposed Order departs from prior FDA practice without acknowledging the change, much less providing a reasoned justification for changing course on prior agency practice. When FDA withdrew the regulatory method for DES, FDA provided the sponsors an opportunity for a hearing on the adequacy of the regulatory method before revoking the method.[37] During the proceeding regarding withdrawal of the DES NADAs, the Commissioner considered (1) whether the original regulatory method was "adequate and practicable for regulatory purposes" and (2) whether there were any other "adequate and reliable methods" that were "practicable for regulatory purposes and capable of detecting and identifying residues in edible tissue resulting from the use of DES at all levels taken as the operational definition of no residue, or at all levels above a level established as a safe tolerance for any noncarcinogenic adverse effects."[38] This process allowed the sponsors to present arguments and evidence concerning the adequacy of the approved method and proposed alternative regulatory methods—just as Phibro seeks to do here.[39]

Ultimately, FDA revoked the DES regulatory method at the same time it ordered withdrawal of the DES NADA approvals.[40] The Commissioner explained that the approved method of detecting DES residues was not adequate for regulatory purposes, and—critically—that there were no other adequate and reliable methods that could meet the statutory requirements of the DES Proviso.[41] Thus, the DES proceeding establishes that the regulatory method and withdrawal of the NADA approvals must be considered together, in a single proceeding, and that FDA cannot revoke the method through an earlier, standalone proceeding. CVM's Proposed Order is unlawful because it departs without explanation from the DES precedent.[42]

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[36] *See FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 514–15 (2009).

[37] *See* FDA, *Diethylstilbestrol; Notice of Hearing On Proposal To Withdraw Approval of New Animal Drug Applications*, 41 Fed. Reg. 52,105, 52,106 (Nov. 26, 1976).

[38] *Id.* at 52,106.

[39] FDA, *Diethylstilbestrol; Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision*, 44 Fed. Reg. 54,852, 54,852, 54856–58 (Sept. 21 1979).

[40] *Id.* at 54,852, 54, 858.

[41] *Id.*

[42] *See Fox Television*, 556 U.S. at 514–15.

B. Alternatively, if FDA finalizes the Proposed Order, the Commissioner should stay the final order's effective date.

If FDA finalizes the Proposed Order, the undersigned requests in the alternative that the Commissioner immediately stay the effect of the final method-revocation order. An immediate stay would be warranted in that circumstance because Phibro's request satisfies all the requirements of § 10.35(d). Each factor is discussed in turn.

1. Phibro and its customers would suffer irreparable injury if a stay is not granted.

Finalizing the Proposed Order without granting an immediate administrative stay would cause significant uncertainty regarding the regulatory status of carbadox and irreparably harm Phibro and its customers.

Carbadox is a crucially important medicine for the U.S. pork industry to help maintain the health and welfare of millions of pigs. Its removal from the market would impose staggering costs on the American economy and the swine industry, which has already been hard hit by the COVID-19 pandemic. Among other things, removing carbadox from the market would cost the U.S. swine industry approximately $5.3 billion over a ten-year period.[43] The major drivers of this cost on an annual basis would be increased swine diseases including those caused by *Brachyspira* (expected to cost $447 million annually), *Salmonella* (expected to cost $119 million annually), and *E. coli* (expected to cost $125 million annually). This high cost is also driven by the lack of effectiveness of the drugs that would be used to replace carbadox, many of which are also medically important to humans, and thus their use could lead to antibiotic resistance of medically important antimicrobials. Other likely impacts include food safety problems caused by infected pigs, higher pig death loss, a reduction in the number of small swine farms, and lower pork quality at higher cost to the consumer.[44]

Similarly, an order revoking the carbadox regulatory method 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. Together with the harms described above, these losses would constitute irreparable harm because they are substantial and the affected parties could not recover them from FDA if the final method-revocation order were later set aside.[45]

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[43] Phibro Comments at 86–88 (citing 2020 analysis by C.F. Grass Consulting, a copy of which is attached as **Exhibit A** to this Petition).

[44] *Id.*

[45] *See, e.g., Mexichem Specialty Resins, Inc. v. EPA*, 787 F.3d 544, 555 (D.C. Cir. 2015) ("Financial injury" may constitute irreparable harm when "no 'adequate compensatory or other corrective relief will be available at a later date.'" (cleaned up)); *Clarke v. Office of Fed. Housing Enter. Oversight*, 355 F. Supp. 2d 56, 65 (D.D.C. 2004) ("[C]ourts have recognized that economic loss may constitute 'irreparable harm' where a plaintiff's alleged damages are unrecoverable.").

Phibro has submitted overwhelming evidence that carbadox is safe and, thus, under FDCA Section 512(e)(1) (21 U.S.C. § 360b(e)(1)), can continue to be lawfully marketed unless and until approval for the carbadox NADAs is withdrawn. Nevertheless, revocation of the approved regulatory method when carbadox is legally required to have such a method could in and of itself raise significant questions regarding whether carbadox would become adulterated during the interim period between issuance of the method-revocation order and the conclusion of a new NADA withdrawal proceeding. This uncertainty surrounding the marketing authorization of carbadox would immediately jeopardize both the ongoing sale and distribution of carbadox as well as its continued use by the swine industry prior to any formal withdrawal of the NADA approvals. These harms justify issuance of a stay, particularly in light of the following considerations:

CVM is not arguing that carbadox is unsafe.

The FDCA prohibits the introduction or delivery for introduction into interstate commerce of any drug that is adulterated, and prohibits the adulteration of any drug that is in interstate commerce.[46] A drug is considered adulterated "if it is a new animal drug which is unsafe within the meaning of section 512" or "if it is an animal feed bearing or containing a new animal drug, and such animal feed is unsafe within the meaning of section 512."[47] Critically important to this analysis is the fact that CVM has abandoned any argument made previously (i.e., in the 2016 NOOH) that carbadox is unsafe. CVM has never taken the position that the marketing or use of carbadox poses an imminent hazard, and as noted above recently issued a Frequently Asked Questions document that affirmatively communicates that consumers should not make dietary changes in connection with the Proposed Order.[48] Having given up any argument that carbadox is unsafe, CVM certainly cannot make that assertion now.

Carbadox is permitted to stay on the market unless and until the carbadox NADA approvals are withdrawn.

Because CVM is not asserting that the drug is unsafe, and, thus, there is no imminent hazard under FDCA Section 512(e)(1) (21 U.S.C. § 360b(e)(1)), CVM must issue and pursue an NOOH before the NADA approvals for carbadox can be withdrawn.

Revoking the regulatory method could be interpreted to mean carbadox could no longer be sold or used.

Despite the FDCA's requirement that the agency hold a hearing before taking an approved drug off the market, the revocation of the approved regulatory method for carbadox raises substantial uncertainty regarding whether CVM views that revocation as a *de facto* determination

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[46] *See* FDCA § 301(a), (b) (21 U.S.C. § 331(a), (b)).

[47] *Id.* § 501(a)(5), (6) (21 U.S.C. §. 351(a)(5), (6)).

[48] *See* FDA, *Questions and Answers regarding Carbadox* (July 17, 2020), https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox (FDA "is not recommending that people make changes in their food choices" in response to CVM's proposal to revoke the approved regulatory method for carbadox).

that carbadox is unsafe under Section 512 because, once FDA takes that step, there would be no approved method that can be used to detect potentially carcinogenic residues. Under Sections 501(a)(5) and (6), an animal drug that is unsafe under Section 512 is itself adulterated and adulterates the animal feed in which it is included. Accordingly, if FDA finalizes the Proposed Order and revokes the regulatory method for carbadox, it could result in a scenario in which carbadox essentially could not be sold or used—even while the carbadox NADA approvals remain in effect—because of the uncertainty regarding whether these actions effectively adulterate both the carbadox itself and the feed into which it is introduced. In that scenario, carbadox would be off the market without Phibro being afforded the due process of a NADA withdrawal proceeding, even when CVM has not raised or proven imminent safety threats.

To be clear, Phibro does not believe that carbadox should be considered adulterated merely by virtue of an order revoking the approved carbadox regulatory method, and Phibro would vigorously assert its rights in court if necessary. However, Phibro recognizes that there might not be a mechanism to promptly clear up uncertainty on the adulteration issue, and that CVM could take a contrary position at any time. Accordingly, to prevent immediate and substantial harm to Phibro and its customers during the interim period between issuance of a final method-revocation order and completion of any new NADA withdrawal proceeding, the Commissioner should immediately stay the effect of any order revoking the carbadox regulatory method pending the outcome of the NADA withdrawal proceeding.

2. Phibro's case is not frivolous, and Phibro is pursuing this stay in good faith.

Phibro's comments show that the two-step approach described in the Proposed Order would improperly avoid consideration of carbadox's safety and areas of scientific disagreement between Phibro and CVM. Although CVM has now abandoned any argument that carbadox is unsafe, CVM nonetheless seeks to revoke the regulatory method and then withdraw marketing authorization for carbadox solely based on the absence of an approved method, without ever addressing the drug's safety or the adequacy of potential alternative methods.

Further, for the reasons given in Part III.A above, the Proposed Order exceeds CVM's authority under the FDCA and applicable FDA regulations, which entitle Phibro to an opportunity for a hearing before an impartial adjudicator on issues related to the withdrawal of the regulatory method. Similarly, longstanding FDA precedent, including the DES proceeding, indicates that those issues must be considered together when determining whether to withdraw a NADA approval.[49] Phibro is unaware of *any* instance in which FDA has taken the two-step approach described in the Proposed Order, and the unprecedented nature of that approach is in itself a strong basis for granting a stay. The fact that CVM proposes to resolve the first phase of that two-step proceeding itself, rather than before an impartial third-party adjudicator, reinforces the need for a stay.

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[49] *See* Phibro Comments at 47–49; 41 Fed. Reg. at 52,105, 54858; 44 Fed. Reg. at 54,852.

Above and beyond these procedural points, Phibro's response to the Proposed Order shows that (1) the approved carbadox regulatory method satisfies all applicable legal requirements and (2) in any event a well-established alternative regulatory method is available.[50] These arguments, too, are substantial and warrant consideration by an impartial adjudicator.

The relevant facts and robust legal arguments Phibro addressed in its comments raise serious questions regarding the legality of revoking the regulatory method without an evidentiary hearing. While FDA has not yet ruled on these arguments, they are not frivolous and Phibro intends to assert them in seeking judicial review of any standalone final order revoking the approved regulatory method.

Moreover, Phibro has demonstrated its good faith in pursuing this stay. The 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. CVM first raised questions regarding Phibro's ability to characterize carbadox residues in December 2011. Phibro thereafter promptly began designing studies and submitting proposals for studies intended to answer CVM's questions. Phibro kept CVM apprised of the progress it was making on the carbadox studies, and informed CVM that the studies would be completed by June 2016. On April 12, 2016, CVM nonetheless issued a NOOH to withdraw carbadox's approvals and remove the drug from the market. Phibro, however, completed its studies on time and submitted the final reports to CVM on July 6, 2016. Five days later, on July 11, Phibro filed its detailed 2016 NOOH Response that discussed Phibro's studies and provided factual evidence contesting CVM's allegations in the 2016 NOOH regarding both adequacy of the method and carbadox's safety. Phibro then responded to nearly 200 questions from CVM about Phibro's studies over the next few years. Phibro estimates that in doing this work, combined with preparing the 2016 Response to the NOOH, it spent several million dollars and—between Phibro, its scientists, and its counsel—hundreds of hours doing so.[51]

CVM has now withdrawn the 2016 NOOH and issued the Proposed Order, seeking to revoke the carbadox regulatory method and thereafter withdraw the carbadox NADA approvals without providing Phibro with an opportunity to be heard before an impartial adjudicator regarding the validity of the current regulatory method, the availability of an alternative regulatory method, or the safety of carbadox. Throughout the proceedings described above, Phibro has acted in good faith, and continues to act in good faith now. Phibro has produced overwhelming evidence that carbadox is safe and that there are suitable methods for detecting residues of carcinogenic concern. Phibro will continue to defend this vitally important drug until it has exhausted all of its remedies. If FDA decides to revoke the approved carbadox regulatory method, the Commissioner should immediately stay the order until after these issues are resolved in a new NADA withdrawal proceeding, as provided for in FDCA Section 512(e) (21 U.S.C. § 360b(e)).

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[50] *See* Phibro Comments at 60–81.

[51] Phibro requested a hearing in the 2016 NOOH proceeding, and CVM agreed that a hearing was warranted with respect to several issues. *See* note 25, *supra*.

3. There are sound public policy grounds supporting the stay.

Public policy arguments strongly support issuance of an immediate stay pending resolution of a new NADA withdrawal proceeding. As discussed above, removal of carbadox from the marketplace would result in significant economic harm and would severely hinder the ability of the swine industry to provide affordable and safe meat.

Issuing a stay would generate several important benefits for FDA as well. To start, a stay would eliminate the need for emergency proceedings on a motion for temporary restraining order (TRO) or preliminary injunction (PI) regarding the validity of a final order revoking the approved carbadox regulatory method. Instead, all judicial review of the agency's decisionmaking would take place *after* completion of a new NADA withdrawal proceeding—thus promoting orderly resolution of the issues, preventing piecemeal litigation, and avoiding needless expenditure of agency resources and taxpayer money on TRO and PI proceedings. This approach would also allow CVM to pursue withdrawal of the NADAs in a new NADA withdrawal proceeding, while preserving Phibro's ability to raise procedural defenses during that proceeding and in any subsequent (post-NADA withdrawal) court proceedings.

Granting the requested stay would therefore (1) allow CVM to move forward in an orderly fashion with a NADA withdrawal proceeding, consistent with past agency practice, (2) avoid needless market uncertainty and irreparable harm to Phibro and its customers during the interim period between issuance of a final method-revocation order and completion of the NADA withdrawal proceeding, and (3) ensure the efficient use of government resources by eliminating the need for immediate emergency judicial review of the unprecedented two-step procedural approach contemplated in the Proposed Order.

Further, as is the case with all medical products that FDA regulates, the agency must determine whether the benefits of the product outweigh its risks. The benefits and risks associated with medical products are not limited to those experienced by the individual humans or animals to which they are administered. Rather, in carrying out its mission to protect and promote the public health, 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. In the case of carbadox, FDA must consider not only the safety and effectiveness of the product for the treatment of swine (both of which are well-established), but also the public health impact of removing the product from the market. Carbadox is effective in treating dysentery and other infections in swine, but it is not a drug that is used to treat human infections. FDA therefore has classified carbadox as not "medically important."[52]

As CVM recently explained when announcing the availability of an October 9, 2020 Concept Paper on antimicrobial resistance (AMR)—the ability of a microorganism to resist the

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[52] *See, e.g.*, FDA, *Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs* (Oct. 9, 2020) (Concept Paper), https://www.fda.gov/media/142846/download.

effects of a drug—AMR is a "growing global threat."[53] The Concept Paper recognizes the need for a comprehensive approach to combatting AMR and discusses a potential approach to assessing whether and to what extent drugs used in animals are important to the treatment of microbial infections in humans.[54] The objective, of course, is to minimize the use in animals of antimicrobial drugs that are medically important to humans to mitigate the public health impact of the use of antibiotics and other antimicrobial products. In the Concept Paper, CVM ranks drugs used in animals by their medical importance in humans and includes carbadox on a short list of the types of products that are *not* medically important to humans.[55] Within that list, CVM places carbadox in "Group 2," meaning not only that the drug is not medically important in humans (the Concept Paper notes that carbadox is not approved for use of any kind in humans, even for treatment of non-serious infections), but also that it has an "extensive history and experience of use in animals."[56] Based on these factors, carbadox is one of only four veterinary drugs that are identified as a "Tier 3" product, meaning that it presents the "lowest impact" on antimicrobial resistance.[57]

If carbadox is removed from the market, farmers who raise swine for the U.S. food supply will have no choice but to switch to alternative products that are, unlike carbadox, medically important human drugs. Reverting to the use of such medically important antibiotics would reverse the tremendous strides Phibro has made in reducing the use of these products in the animal supply, as the Federal Task Force on Combating Antibiotic-Resistant Bacteria (CARB Task Force) reported in the five-year plan that it released on the same day as FDA's Concept Paper.[58]

It is thus crucially important that FDA's benefit-risk assessment for carbadox take into account not only the effectiveness of carbadox for its intended use and the fact that it has an extensive history of safe use, but also the downside risks of effectively encouraging the use of medically important human drugs in place of carbadox. FDA has rightly described the AMR concern as "a serious, complex and costly public health problem."[59] Any effort by CVM to continue

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[53] FDA, *Antimicrobial Resistance* (Oct. 9, 2020), https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance.

[54] *See* Concept Paper at 1.

[55] Concept Paper at 9–17.

[56] Concept Paper at 5, 17

[57] *See* Concept Paper at 4.

[58] *See* Federal Task Force on Combating Antibiotic-Resistant Bacteria, *National Action Plan for Combatting Antibiotic-Resistant Bacteria 2020-2025* (Oct. 9, 2020), at 12 (describing governmental efforts to bring "together producers, veterinarians, and feed suppliers to create a shared understanding of these new initiatives and to discuss the management challenges to implementing them" and highlighting "a 38 percent decline between 2015 and 2018 in medically important antibiotics sold for use in food-producing animals").

[59] *See* FDA, *Antimicrobial Resistance Information from FDA* (Oct. 30, 2020), https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/antimicrobial-resistance-information-fda.

on its course to remove carbadox from the market must take into consideration the significant impact that such a step would have on the use of human antimicrobial products regulated by FDA's Center for Drug Evaluation and Research, as well as the important strategic goals of the CARB Task Force.

4. The delay resulting from the stay is not outweighed by public health or other public interests.

There are no public health interests that weigh in favor of denying Phibro's petition for an administrative stay. Carbadox has been on the market for nearly 50 years without any evidence of harm either to pigs or to the public. As Phibro has demonstrated, carbadox is safe. In fact, the Proposed Order expressly abandons any challenge to the general safety of carbadox. If the Proposed Order is finalized, CVM has stated it will issue a NOOH seeking to withdraw approval of the carbadox NADAs *not* because carbadox is unsafe, but because carbadox would no longer have an approved regulatory method as required by the DES Proviso. The question whether the carbadox regulatory method is adequate (and, if necessary, whether to adopt the alternative method proposed in Phibro's comments) should be resolved during the NADA withdrawal proceeding, and not before that proceeding begins. Therefore, the Commissioner should stay any revocation of the regulatory method until after the conclusion of a future proceeding regarding withdrawal of approval for the carbadox NADAs.

IV. Conclusion

For the foregoing reasons, the Commissioner should refrain from finalizing, and withdraw, the Proposed Order seeking to revoke the approved carbadox regulatory method. Alternatively, if FDA finalizes the Proposed Order, the Commissioner should immediately stay the effect of the final order revoking the regulatory method until after completion of any proceedings regarding withdrawal of the carbadox NADA approvals.

V. Environmental Impact

This petition is categorically excluded from the requirement for an environmental assessment or environmental impact statement under 21 C.F.R. § 25.33.

VI. Certification

Pursuant to 21 C.F.R. § 10.30(b), the undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Respectfully submitted,

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