IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

PHIBRO ANIMAL HEALTH CORPORATION,
300 Frank W. Burr Blvd., Suite 21
Teaneck, New Jersey 07666

Plaintiff,

v.

U.S. FOOD AND DRUG ADMINISTRATION,
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

ROBERT M. CALIFF, in his official capacity as Commissioner of Food and Drugs,
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

CENTER FOR VETERINARY MEDICINE,
7519 Standish Place
Rockville, Maryland 20855

TRACEY FORFA, in her official capacity as Director of the Center for Veterinary Medicine,
7519 Standish Place
Rockville, Maryland 20855

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES,
200 Independence Avenue, SW
Washington, DC 20201

XAVIER BECERRA, in his official capacity as Secretary of Health and Human Services,
200 Independence Avenue, SW
Washington, DC 20201

Defendants.

Civil Case No. _____

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

Plaintiff Phibro Animal Health Corporation ("Phibro") brings this suit against Defendants U.S. Food and Drug Administration ("FDA"); Robert M. Califf, in his official capacity as Commissioner of Food and Drugs; Center for Veterinary Medicine; Tracey Forfa, in her official capacity as Director of the Center for Veterinary Medicine; U.S. Department of Health and Human Services; and Xavier Becerra, in his official capacity as Secretary of Health and Human Services (collectively, "Defendants"), and alleges as follows:

INTRODUCTION

1. This suit seeks judicial review of two FDA orders regarding carbadox, an animal drug marketed by Phibro and used to protect newborn pigs from serious, life-threatening diseases. FDA's orders are unlawful because they rely on procedural maneuvers that eviscerate Phibro's rights under the Federal Food, Drug, and Cosmetic Act ("FDCA") and its implementing regulations. Rather than turning square corners, as the Administrative Procedure Act ("APA") requires, FDA took shortcuts by issuing its orders without conducting an evidentiary hearing mandated by statute and departed from longstanding agency precedent—all to produce a predetermined outcome.

2. Carbadox has been approved by FDA for more than a half century and has been in widespread use throughout that time. FDA reiterated that carbadox is safe and effective as recently as 2004, when it approved a new carbadox product, and pork producers nationwide rely on carbadox to treat more than 35 million pigs each year.

3. Despite carbadox's long track record and importance to industry, FDA—acting through its Center for Veterinary Medicine ("CVM")—now seeks to take the drug off the market. For decades, the agency has identified carbadox as a potential carcinogen at high concentrations,

based on studies involving high doses administered to rodents under laboratory conditions, but also concluded that carbadox is safe when used as labeled, for both pigs and humans who consume pork products. The FDA orders at issue in this lawsuit do not disturb that longstanding safety conclusion; indeed, FDA's website advises consumers that there is no need to "make changes in their food choices" as a result of the action taken in these proceedings. Instead, the challenged FDA orders focus on the validity of a testing procedure—known as a "regulatory method"—used to detect the presence of carbadox residues when pork products enter the food supply, thus ensuring that the residues are at or below the FDA-determined safe level. FDA adopted a regulatory method for carbadox when the drug was initially approved, as required by the FDCA, and in 1998 adopted an updated regulatory method based on new, more accurate testing protocols.

4. The orders under review conclude that FDA erred when it approved the updated carbadox regulatory method in 1998. According to the orders, there is not enough data to show that the 1998 regulatory method satisfies obscure provisions of the Code of Federal Regulations regarding measurement of "marker residues," and the testing protocols used by the U.S. Department of Agriculture ("USDA") and the Canadian Food Inspection Agency (both of which Phibro proposed as alternatives to the 1998 method) likewise fail to satisfy those regulations. The orders thus rescind FDA approval for the carbadox regulatory method, effective immediately. *See Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method*, 88 Fed. Reg. 76,760 (Nov. 7, 2023) (the "Revocation Order"); Final Response Letter from FDA Center for Veterinary Medicine, Docket FDA-2020-P-2312 (Nov. 2, 2023) (the "Citizen Petition Denial Order," and together with the Revocation Order, the "Challenged Orders"), *available at* https://www.regulations.gov/document/FDA-2020-P-2312-0005.

5. By FDA's own admission, the agency revoked its approval of the carbadox regulatory method as the first step in a two-step scheme designed to take carbadox off the market entirely. That scheme hinges on FDCA provisions directing that Phibro cannot sell carbadox products without an FDA-approved regulatory method. *See* 21 U.S.C. §§ 360b(a)(1), 360b(d)(1)(I), 331. On the same day that it issued the Challenged Orders, FDA cited that statutory requirement as the sole basis for a new administrative proceeding (now underway) in which the agency proposes to withdraw the marketing approvals for all carbadox products—i.e., to prohibit the sale of carbadox in interstate commerce. In other words, FDA has relied on its revocation of the regulatory method as the reason to remove carbadox from the market.

6. The question at the heart of this lawsuit is whether FDA acted lawfully in revoking its longstanding approval of the carbadox regulatory method. The answer is no. FDA has never before sought to withdraw approval for an animal drug through the two-step scheme adopted in the Challenged Orders, and as demonstrated below, those orders are arbitrary, capricious, and contrary to law.

7. *First*, the Challenged Orders unlawfully deprive Phibro of its right to a formal evidentiary hearing regarding the validity of the carbadox regulatory method. The FDCA and FDA's own regulations mandate that the agency must provide the sponsor of an approved animal drug an opportunity for a formal evidentiary hearing before withdrawing the drug from the market. *See, e.g.*, 21 U.S.C. § 360b(e)(1). This procedural safeguard ensures that a drug will not be summarily removed from the market without a meaningful opportunity to test the basis for FDA's action. Although Phibro requested an evidentiary hearing regarding the carbadox regulatory method, FDA refused to provide one.

8. By proceeding in this manner, FDA has determined—in advance, and without an evidentiary hearing—the question that would be most central to any evidentiary hearing on the withdrawal of carbadox from the market: whether there is an adequate regulatory method for detecting carbadox residues. Phibro presented extensive scientific data and expert testimony showing that the method FDA approved in 1998 satisfies all applicable regulatory requirements, and that alternative methods are available as well. Yet FDA rejected those submissions in the Challenged Orders and credited CVM's competing assertions *without* affording Phibro an opportunity for an evidentiary hearing. Although FDA has said that Phibro may submit "new or additional data" in the new (and ongoing) proceeding regarding outright withdrawal of carbadox from the market, that limitation ensures that any future hearing will be drained of its core purpose: to test the validity of FDA's conclusions regarding the regulatory method, including with respect to the data Phibro has *already* provided. As to *that* data, the Challenged Orders have resolved, through an informal procedure, issues that must, by statute and regulation, be adjudicated through a formal evidentiary hearing. In other words, the best-case scenario for Phibro is a future "evidentiary" hearing where the vast majority of the evidence undermining FDA's justification for withdrawing carbadox will be off the table. FDA's novel two-step approach deprives Phibro of its right to present its evidence and challenge the basis for FDA's action through an evidentiary hearing, in contravention of the FDCA and FDA's regulations.

9. The two-step procedure adopted by the Challenged Orders is particularly problematic because the agency engineered it to circumvent Phibro's hearing rights. CVM first initiated a procedure to remove carbadox from the market in 2016. But after Phibro submitted its evidence reaffirming the safety of carbadox and invoked its right to a formal evidentiary hearing, and after CVM acknowledged that a hearing was warranted, CVM voluntarily dismissed the 2016

proceeding. Rather than defending its position, CVM initiated a new round of proceedings—the ones at issue in this suit—designed to mount a collateral attack on carbadox's marketing authorization by revoking the regulatory method on which that authorization depends. The agency denied Phibro's request for a formal evidentiary hearing regarding the regulatory method in the proceedings below, and has now initiated yet another proceeding (regarding whether to withdraw marketing approval for carbadox altogether) in which the key issue—the availability of a regulatory method—has already been decided. The Challenged Orders thus pave the way for FDA to take carbadox off the market without *ever* granting Phibro the formal evidentiary hearing it has twice requested and is entitled by law to receive. The D.C. Circuit has ruled against FDA in prior animal drug cases based on the agency's failure to afford the sponsor the hearing it was due, *see Hess & Clark, Div. of Rhodia, Inc. v. FDA*, 495 F.2d 975 (D.C. Cir. 1974); *Chemetron Corp. v. U.S. Dept. of Health, Educ., and Welfare*, 495 F.2d 995 (D.C. Cir. 1974), and the same result is warranted here.

10. *Second*, the Challenged Orders are invalid because the proceedings below failed to comply with the impartiality requirements of the FDCA, FDA's regulations, the APA, and due process. Those bodies of law mandate that adjudication of a drug manufacturer's rights be conducted by a neutral decisionmaker who has not been involved in prosecuting the enforcement proceeding. FDA violated that rule here by allowing CVM—the agency component that proposed to revoke approval for the carbadox regulatory method—to both prosecute the action and shape the decision, without any meaningful separation of functions between adjudicative and investigational personnel.

11. Making matters worse, CVM predetermined the outcome of the proceedings below. Before, during, and after those proceedings, the agency publicly announced that it was "working

to remove [carbadox] from the market." An agency spokesperson likewise told the press that revoking approval for the regulatory method was the "most straightforward and least resource-intensive process for removing carbadox from the market." Records obtained through the Freedom of Information Act show that this bias permeated the proceedings: CVM officials remarked to one another that it was a "big waste of time" to consider Phibro's evidence, that "we aren't changing our mind," and that revocation of the regulatory method was "inevitable." During a public meeting regarding the carbadox regulatory method, the officials exchanged Internet memes lampooning Phibro's representative while she presented the company's evidence and legal arguments, including this image:

12. Together, this evidence shows that FDA reviewed the carbadox regulatory method with an inalterably closed mind, depriving Phibro of its right to a fair process driven by the facts and the law rather than preconceived notions about the right outcome.

13. *Third*, the Revocation Order is arbitrary and capricious because it departs from longstanding precedent under which FDA has addressed withdrawal of animal drug approvals and revocation of regulatory methods together, rather than separately. Indeed, this proceeding marks the first time that FDA has *ever* bifurcated those issues. Moreover, as noted above, when FDA previously sought to withdraw approval for an animal drug without holding a formal evidentiary hearing addressing the basis for the withdrawal, the D.C. Circuit set aside the agency's action. FDA later remedied that error by providing the drug sponsors with a hearing, and it has not adequately justified its abandonment of that precedent here.

14. *Fourth*, the Challenged Orders are arbitrary and capricious because their conclusions are contrary to the record, which shows that the regulatory method FDA approved in 1998 remains appropriate, and that there are suitable alternative methods available as well.

15. As to the 1998 method, Phibro presented ample evidence that the "marker residue" can be measured in a way that satisfies FDA's regulations, including by demonstrating that carbadox residues reach (and fall well below) the FDA-determined safe concentration level long before pork products enter the food supply. The Challenged Orders reject that evidence because, in CVM's view, Phibro's data does not account for short-lived intermediate carbadox metabolites. That rationale fails because the record shows that these metabolites degrade rapidly, such that *months* before pigs are slaughtered, any remaining metabolites are either safe or are well below the FDA-determined safe level. CVM likewise erred by presuming that carbadox residues bound to tissue proteins are harmful and therefore must be counted in determining whether the total

amount of residue (the focus of FDA's regulations) falls below the safe concentration level. That presumption is at odds with longstanding FDA practice and settled scientific consensus that carbadox residues bound to animal tissues are incapable of causing harm to human consumers. Regardless, Phibro presented extensive evidence, including expert reports, showing that long before pigs go to market, the only bound residue present is a compound FDA acknowledges presents no danger to human health.

16. As to the alternatives proposed by Phibro, the Challenged Orders fail to provide a reasonable explanation for rejecting the testing methods employed by the U.S. Department of Agriculture and the Canadian Food Inspection Agency. Both of those alternative methods are in use today, and the record shows that both of them are capable of accurately and consistently detecting when carbadox residues reach (and go below) the safe concentration level. CVM rejected these methods in passing, based on a single, threadbare rationale: According to the agency, there is not enough data to establish a "marker residue" as required by FDA regulations. That argument fails for the reasons given above and is particularly arbitrary in light of evidence showing that CVM itself has acknowledged that the Canadian method "has been used successfully for many years." Additionally, USDA used its method even when the FDA regulatory method was in place and continues to use its method today after FDA revoked the regulatory method in the proceedings at issue here.

17. The Challenged Orders, in short, override important procedural protections for the purpose of lessening the burden on the agency and producing a predetermined result. For that reason and the other reasons discussed below, the Court should set aside the Challenged Orders and remand for further proceedings. If FDA persists in seeking to rescind the carbadox regulatory

method, the adjudication of that matter must include a formal evidentiary hearing before an impartial decisionmaker that addresses all of the available evidence.

JURISDICTION AND VENUE

18. This Court has subject-matter jurisdiction under 28 U.S.C. § 1331 because this action arises under the United States Constitution, the FDCA, 21 U.S.C. § 360b, and the APA, 5 U.S.C. §§ 701–06.

19. This Court has authority to grant declaratory and injunctive relief pursuant to the Declaratory Judgment Act, 28 U.S.C. §§ 2201–02, the APA, 5 U.S.C. § 702, and the Court's inherent equitable powers.

20. Venue is proper in this District pursuant to 28 U.S.C. § 1391(e)(1) because all defendants are either officers or employees of agencies of the United States acting in their official capacities or agencies of the United States, and a substantial part of the events or omissions giving rise to the claims asserted arose in this District.

21. The Revocation Order constitutes "final agency" action under the APA, 5 U.S.C. § 704, because it completes FDA's decisionmaking process regarding the carbadox regulatory method and has immediate legal consequences for Phibro—including by eliminating a necessary prerequisite for Phibro to market carbadox products. Further, the Revocation Order is a "declaratory order" under the APA that is not subject to the FDCA's special statutory review procedure. *See* 88 Fed. Reg. at 76,762 (citing 5 U.S.C. § 554(e)). That procedure governs FDA actions disapproving or withdrawing approval of New Animal Drug Applications ("NADAs"), as to which review lies exclusively in the courts of appeals. *See* 21 U.S.C. §§ 360b(h), 355(h). By contrast, FDA declaratory orders are "not reviewable in the court of appeals" but are instead "reviewable by the district court under the Administrative Procedure Act." *Weinberger v. Hynson,*

Wescott & Dunning, Inc., 412 U.S. 609, 627 (1973). Review of FDA's Revocation Order is therefore properly before this Court. *See* 5 U.S.C. § 703.

22. The Citizen Petition Denial Order is likewise a "final agency action" under the APA. 5 U.S.C. § 704. FDA regulations provide that a "final decision" disposing of a citizen petition "constitutes final agency action (reviewable in the courts under 5 U.S.C. § 701 *et seq.* and, where appropriate, 28 U.S.C. § 2201)." 21 C.F.R. § 10.45(d). Review of the Citizen Petition Denial Order is therefore properly before this Court. *See* 5 U.S.C. § 703.

PARTIES

23. Plaintiff Phibro Animal Health Corporation is a Delaware corporation headquartered in Teaneck, New Jersey. Phibro develops, manufactures, and markets animal health and nutrition products. Phibro is the owner of NADA Nos. 041-061, 092-955, and 141-211 relating to carbadox, an antimicrobial drug used to treat dysentery, bacterial enteritis, and other conditions in swine.[1] FDA approved the first carbadox NADA in 1972 and has granted additional approvals for carbadox products several times since, most recently in 2004. Phibro markets carbadox under the trade name Mecadox®, and for use in various products that combine carbadox with other animal drug products.

24. Defendant FDA is an agency of the United States within the U.S. Department of Health and Human Services, with delegated responsibility for administering the FDCA and its implementing regulations.

[1] Pfizer Inc., a Delaware corporation that is not a party to this litigation, was previously the owner of the carbadox NADAs.

25. Defendant Robert M. Califf is the Commissioner of Food and Drugs, with delegated responsibility for administering the FDCA and its implementing regulations. Commissioner Califf is sued in his official capacity.

26. Defendant CVM is a branch of FDA with delegated responsibility for administering relevant provisions of the FDCA and its implementing regulations, including provisions relating to animal drugs. CVM is the FDA component that, since 2016, has sought to remove carbadox from the market, including through revocation of the carbadox regulatory method.[2]

27. Defendant Tracey Forfa is Director of CVM, with delegated responsibility for administering relevant provisions of the FDCA and its implementing regulations, including provisions relating to animal drugs. Director Forfa is sued in her official capacity.

28. Defendant U.S. Department of Health and Human Services is an agency of the United States, with ultimate responsibility for administering the FDCA and its implementing regulations.

29. Defendant Xavier Becerra is the Secretary of the U.S. Department of Health and Human Services, with ultimate responsibility for the Department's operations, including its administration of the FDCA and implementing regulations. Secretary Becerra is sued in his official capacity.

STATUTORY AND REGULATORY BACKGROUND

I. The Federal Food, Drug, and Cosmetic Act

30. The Secretary of Health and Human Services, "through the Commissioner" of Food and Drugs, 21 U.S.C. § 393(d)(2), regulates medicated animal feed (that is, animal feed containing

[2] This Complaint uses "FDA" to refer to FDA or CVM except where the distinction matters.

a "new animal drug") under Section 512 of the FDCA, 21 U.S.C. § 360b, among other provisions. *See id.* § 321(v) (defining "new animal drug").

31. Subject to exceptions not relevant here, the FDCA prohibits the sale in interstate commerce of any animal drug that has not been approved by FDA. *See* 21 U.S.C. §§ 331, 351(b)(5)–(6), 360b(a)(1)(A) & (a)(2)(A)(i).

32. The Commissioner of Food and Drugs has delegated to the CVM Director authority to perform all functions relating to approval of new animal drug applications and supplemental applications, *see* FDA, Staff Manual Guides, § 1410.502, as well as authority to "[i]ssue notices of opportunity for a hearing on proposals to refuse approval or to withdraw approval of new animal drug applications," *id.* § 1410.503.

a) Procedure for Approval of New Animal Drugs

33. To obtain approval to market and sell a new animal drug, the drug's sponsor must submit to FDA a New Animal Drug Application, or "NADA." *See* 21 U.S.C. § 360b(b). As part of the NADA, the sponsor must provide, among other things, details about the composition of the drug and full reports of investigations showing that the drug is safe and effective for its intended use. *See id.* § 360(b)(1); 21 C.F.R. § 514.1.

34. FDA evaluates the sponsor's submission and "shall" approve the NADA if it establishes, among other things, that the drug is safe and effective for its intended use. 21 U.S.C. § 360b(c)(1). FDA must refuse to approve a NADA if it finds, "after [providing] due notice to the applicant" and "giving [the applicant an] opportunity for a hearing," that the application does not establish the drug's effectiveness and safety for its intended use. *Id.* § 360b(d)(1)(A)-(E).

35. Generally, under what is known as the Delaney Clause, FDA must also refuse to approve a NADA if it finds, "after [providing] due notice to the applicant" and "giving [the

applicant] an opportunity for a hearing," that the new animal drug "induces cancer" in humans or animals. 21 U.S.C. § 360b(d)(1)(I).

36. However, a new animal drug with cancer-causing potential may be eligible for approval if it satisfies what is known as the Diethylstilbestrol ("DES") Proviso. *See id.* Under the DES Proviso, the Delaney Clause "shall not apply," and a potentially carcinogenic animal drug may be approved, if FDA finds that, under conditions reasonably expected to be followed in practice: (a) the drug "will not adversely affect the animals for which it is intended" and (b) "no residue of such drug will be found," using "methods of examination prescribed or approved by [FDA]," "in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals." *Id.*

37. The DES Proviso thus directs that an animal drug may be approved, despite being a potential carcinogen, if it will be used in a manner that will not "adversely affect" treated animals *and* no residues of the drug "will be found" in food products derived from those animals, using an FDA-approved testing method. Together, these requirements allow for approval of drugs that qualify as potential carcinogens in a laboratory setting, but do not present health risks to animals or humans under real-world conditions.

38. Congress deliberately struck a delicate balance when it amended the Delaney Clause in 1962 to include the DES Proviso. *See, e.g.*, U.S. Dept. of Justice, Office of Legal Counsel, *The Food and Drug Administration's Discretion to Approve Methods of Detection and to Define the Term 'No Residue' Pursuant to the Federal Food, Drug, and Cosmetic Act*, 19 OLC Op. 247 (Oct. 13, 1995), *available at* https://www.justice.gov/file/20181/download ("OLC Opinion") (tracing legislative history of Delaney Clause and DES Proviso). Relevant here, the DES Proviso's requirement that no residues "will be *found*," 21 U.S.C. § 360b(d)(1)(I) (emphasis

added), "contemplates that a [new animal drug] will be approved as long as an approved method *detects* no residue, even though this does not affirmatively mean that no residue was *present* at all"—for example, if "a [residue] level . . . below the sensitivity of the approved method" remains, OLC Opinion at 255 (emphases added). That approach recognizes that many potential carcinogens "when used properly, pass quickly out of the treated animal's system," "leave no detectable residue in edible tissue, and do not harm the animal" or present risks to human health. *Id.* at 248 (citing *Hess & Clark*, 495 F.2d at 979). The DES Proviso thus acknowledges that de minimis, undetectable residue levels are not a reason to keep an otherwise safe and effective drug off the market.

39. FDA regulations implement the FDCA's requirements in two principal ways. *First*, the regulations require a drug's sponsor to propose a "regulatory method," consisting of "procedures for measuring and confirming the presence of" certain of the drug's residues in an animal's tissues. 21 C.F.R. § 500.82(b). This method "must be able to confirm" that residues of carcinogenic concern in designated animal tissues are at or below a safe level, as determined by FDA, and that no such residues are detectable when an animal is slaughtered. *Id.* §§ 500.84(c)(3), 500.88(b). FDA validates proposed regulatory methods using the following approach:

a. FDA begins by studying a drug's potentially carcinogenic residues and typical human diets to determine the total (cumulative) concentration of residues in the human diet, known as S_o, at which there is "no significant increase in the risk of cancer to the human consumer." *Id.* §§ 500.82(b), 500.84(c)(1).

b. FDA next translates the S_o value into S_m, the "concentration of a residue of carcinogenic concern in a specific edible [animal] tissue corresponding to no significant increase in

the risk of cancer to the human consumer," as defined above. *Id.* As a practical matter, S_m represents the level of drug residues determined by FDA to be safe to humans.

c. FDA then identifies a "marker residue," a residue "whose concentration is in a known relationship to the concentration of the residue of carcinogenic concern in the last tissue to deplete to its S_m," and establishes an R_m value corresponding to "the concentration of the marker residue in [a] target [animal] tissue when the residue of carcinogenic concern is equal to S_m." *Id.* §§ 500.82(b), 500.84(c)(2). In other words, FDA identifies a substance to test for that has a known relationship to the residue of carcinogenic concern and then sets a level of that substance (R_m) at which one can know with certainty that the drug's residues are at or below the S_m safe level in all of an animal's edible tissues.[3] *See id.* § 500.86(c) (test result showing marker residue level at or below R_m "can be taken as confirmation that the residue of carcinogenic concern does not exceed S_m in each of the edible tissues," and therefore that products from the animal tested do not present a cancer risk to humans).

d. FDA also identifies the limit of detection, or "LOD," for the regulatory method, defined as "the lowest concentration of" the marker residue "that can be confirmed by the approved regulatory method." *Id.* § 500.82(b). The regulatory method's limit of detection "must be less than or equal to R_m," *id.* § 500.84(c)(2)—otherwise, the method would be incapable of confirming that the residue level in animal tissues is at or below the S_m safe level.

[3] Sometimes, this process measures the residue of carcinogenic concern directly (i.e., the marker residue is the same as the residue of carcinogenic concern, and S_m is the same as R_m), but in other instances a different substance with a known relationship to the residue of carcinogenic concern is used (e.g., because this substance is easier to measure or can be measured more accurately).

40. *Second*, the regulations prescribe a withdrawal period for the drug—a minimum duration of time that must elapse between the last administration of the drug and the date on which the animal is slaughtered, to allow adequate time for the drug to be fully metabolized and reach a point at which it will no longer be found in the animal's tissues using the approved regulatory method. *See id.* §§ 500.82(b), 500.84(c)(3).

41. Under the regulations, the statutory requirement that "no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary . . .) after slaughter," 21 U.S.C. § 360b(d)(1)(I), is deemed to be met when "the marker residue is below the limit of detection using the approved regulatory method," 21 C.F.R. § 500.82(b). This "operational definition of no residue" is accordingly "satisfied when no residue of the compound [of carcinogenic concern] is detectable (that is, the marker residue is below the [limit of detection]) using the approved regulatory method under the conditions of use of the sponsored compound, including any required preslaughter withdrawal period."). *Id.* §§ 500.84(c)(3), 500.88(a). In other words, if the quantity of a residue in animal tissue is so miniscule that the FDA-approved testing method cannot detect it, the residue cannot "be found" within the meaning of the DES Proviso.

42. In simplified terms, the FDA regulations (a) identify a safe level of a potentially carcinogenic drug's residues, (b) require a testing method capable of detecting the residues at or below that safe level, (c) deem that "no residue of such drug will be found" when the potentially carcinogenic residues can no longer be found by using that testing method, and (d) prescribe a minimum waiting period between the last administration of the drug and slaughter of the animal to ensure that no detectable amount of the drug's residues will remain when animal products enter the food supply.

43. To illustrate how these regulations operate in practice, consider a hypothetical cattle drug that qualifies as a potential carcinogen under laboratory conditions. Suppose further that steaks from cows treated with the drug are shown to be safe for human consumption so long as they contain ten parts per million (or less) of the drug's residues, and that studies show that residue levels in the cow's tissues fall below ten parts per million 30 days after the drug is administered. The requirements of the DES Proviso and FDA's regulations will be satisfied if the drug's sponsor identifies a regulatory method capable of reliably detecting the drug's residues at or below ten parts per million, cows treated with the drug are slaughtered at least 30 days after receiving the last dose of the drug, *and* no residue (even below the safe level) will be detected by the regulatory method at the time of slaughter.

44. FDA applies these criteria by requiring drug sponsors to "submit for evaluation and validation" a "regulatory method developed to monitor compliance with FDA's operational definition of no residue," as defined above. 21 C.F.R. § 500.88(a). After FDA has evaluated and validated a sponsor's proposed regulatory method, "FDA will publish in the Federal Register the complete regulatory method for ascertaining the marker residue [level] in the target [animal] tissue." *Id.* § 500.88(c).

45. Pursuant to the DES Proviso, a new animal drug with carcinogenic potential may not be approved unless and until FDA has approved a regulatory method. *See* 21 U.S.C. § 360b(d)(1)(I).

46. If FDA has approved and published a regulatory method for a drug that otherwise has carcinogenic potential, and FDA finds, after notice and a hearing, that no other ground for refusing the sponsor's NADA as set out in 21 U.S.C. § 360b(d)(1)(A)–(I) applies, the Secretary "shall issue an order approving the application," *id.* § 360b(d)(1).

b) Procedure for Withdrawal of Approval for New Animal Drugs

47. The FDCA prescribes procedures FDA must follow when seeking to remove an approved animal drug from the market. In particular, the statute mandates that FDA "shall" provide the owner of an approved NADA "notice and opportunity for hearing" before issuing "an order withdrawing approval of" the NADA. 21 U.S.C. § 360b(e)(1).

48. The FDCA likewise prescribes substantive criteria for withdrawing approval of previously approved animal drugs. FDA "shall" withdraw its prior approval of a NADA if, among other things, new information shows that (a) the drug is not safe or (b) the drug was approved under the DES Proviso but is no longer covered by that provision, such that disapproval is required under the Delaney Clause. *Id.* § 360b(e)(1)(B) (requiring withdrawal of approval where the Secretary finds" that "subparagraph (I) of paragraph (1) of subsection (d) applies to such drug"); *see also id.* § 360b(d)(1)(I) (Delaney Clause "shall not apply" when requirements of DES Proviso are met). An approved animal drug becomes ineligible for the DES Proviso if new information establishes that the drug adversely affects the animals for which it is intended, or that there is no method available to confirm that no residue of the drug will be found in any edible portion of such animals after slaughter. *Id.* §§ 360b(d)(1)(I), (e)(1).

49. When FDA proposes to exercise its authority to withdraw approval of a previously approved animal drug, the NADA owner may request a hearing on the proposal within 30 days. *See* 21 C.F.R. §§ 12.21(b), 12.22(b), 514.201.

50. The NADA owner's hearing request "will be granted" so long as "[t]here is a genuine and substantial issue of fact for resolution," evidence is available to resolve that issue, and additional requirements are satisfied. *Id.* § 12.24(b)(1)–(6).

51. The hearing "shall be governed" by the procedural protections set forth in Part 12 of FDA's regulations. 21 C.F.R. § 514.201. For example:

a. In advance of the hearing, FDA is required to disclose a witness list, all documents containing relevant factual information "whether favorable or unfavorable to the director's position," and "[a]ll other documentary data and information relied upon," among other things, *id.* §§ 12.85(a), 12.92(a);

b. At the hearing, the NADA owner is afforded the opportunity to present testimony and cross-examine adverse witnesses, *see id.* §§ 12.70(b), 12.87(b)(1), 12.89(b), 12.94(d);

c. Evidence and testimony presented at the hearing may be excluded if "irrelevant, immaterial, unreliable, or repetitive," and the presiding officer must "exclude irrelevant or repetitious" examination, *id.* § 12.94(c)(1)(i), (d)(1)(i), (f);

d. The participation of nonparties is limited. For example, nonparties may not "[s]ubmit written interrogatories" or "[c]onduct cross-examination," and under no circumstances may the rights of a nonparty "exceed the rights of a party." *Id.* § 12.89(b), (d).

52. Further, in a hearing conducted under FDA's Part 12 regulations, the adjudicator must be impartial. The presiding officer must be the Commissioner of Food and Drugs, a delegated member of the Commissioner's office, or an administrative law judge qualified under 5 U.S.C. § 3105. *See* 21 C.F.R. § 12.60. And FDA's rules establish a strict separation of functions between the investigative and adjudicative personnel involved in conducting such a hearing. *See id.* § 10.55(b)(2)(i). This arrangement ensures that the FDA sub-agency seeking to withdraw the NADA approval (i.e., CVM) is not also the decision maker regarding disputed scientific and legal issues raised at the hearing.

53. Following briefing and oral argument, the presiding officer must prepare and file an initial decision, which must include the officer's findings of fact, conclusions of law, a discussion of the reasons for the findings and conclusions, citations to the record supporting the findings and conclusions, an appropriate regulation or order, and an effective date for any regulation or order issued. 21 C.F.R. § 12.120. A participant may appeal the presiding officer's initial decision to the Commissioner, *id.* § 12.125, who must then issue a final decision, *see id.* § 12.130. The Commissioner's decision is final agency action subject to judicial review under the APA. *See id.* § 12.140; *see also* 21 U.S.C. § 360b(h).

54. FDA precedent illustrates how these rules operate in practice. In the 1970s, FDA addressed concerns regarding diethylstilbestrol (DES), a potentially carcinogenic animal drug that was originally approved in the 1950s. Although FDA initially failed to afford the DES sponsors the hearing they were due, the D.C. Circuit ruled against FDA in a pair of companion cases decided together, *see Hess & Clark*, 495 F.2d 975; *Chemetron Corp.*, 495 F.2d 995, and FDA remedied its error by providing the sponsors with a formal evidentiary hearing governed by the procedural requirements noted above.

55. Specifically, DES was first approved as an animal drug in 1954, and in 1963, FDA published regulations establishing a method for detecting, identifying, and measuring DES residues. Thereafter, however, a "new and more sensitive method" arose showing greater DES residues in animal livers than originally assumed. *Diethylstilbestrol; Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Animal Drug Applications*, 37 Fed. Reg. 12,251, 12,252 (June 21, 1972). This development led FDA to issue "an opportunity for a hearing on a proposal to withdraw approval" of the DES NADAs because of its concerns with the sensitivity of the then-approved method. *Id.* at 12,252. FDA ultimately denied requests for a

hearing, revoked the DES method regulations, and withdrew approval for the DES NADAs. *See* 37 Fed. Reg. 15,747 (Aug. 4, 1972); *Order Denying a Hearing and Withdrawing Approval of New Animal Drug Applications for Diethylstilbestrol*, 38 Fed. Reg. 10,485 (Apr. 27, 1973).

56. The D.C. Circuit vacated those withdrawal orders because FDA gave inadequate notice of its proposals. *See Hess & Clark*, 495 F.2d at 980–81. In so doing, the court expressly rejected FDA's attempts to bifurcate consideration of the regulatory method and NADA withdrawals, explaining that the method revocation was "inextricably united to . . . withdrawal of approval," such that the FDCA "*require*[*s*] the Commissioner to revoke [regulatory methods] *when* he revokes approval of an NADA." *Id.* at 995. The court further explained that where new evidence suggested that the approved method is insufficient to detect the residue marker, a hearing is the appropriate process. *See Chemetron Corp.*, 495 F.2d at 999 (new evidence from a method "detect[ing] residues" is a "basic matter . . . requiring a hearing").

57. On remand, FDA provided an opportunity for public comment on the regulatory method for DES residues. And, after receiving comments on the issue, FDA did not simply revoke the method: The agency issued a notice of opportunity for a formal evidentiary hearing proposing to withdraw the DES NADAs on the grounds that the Delaney Clause applied and DES had not been shown to be safe for its intended use. *See Diethylstilbestrol; Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Animal Drug Applications*, 41 Fed. Reg. 1804, 1806 (Jan. 12, 1976).

58. In response to comments suggesting "that the official methodology might be an issue for a hearing rather than the subject of revocation before a hearing," the Commissioner agreed that "the opportunity for [a] 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." *Id.* at 1805. Sponsors were then invited to "provid[e] a well-organized and *full-factual* analysis" justifying their request for a hearing, *id.* at 1807—the sponsors were not limited to "new" evidence that FDA had not yet considered. The sponsors requested a hearing, which FDA granted with respect to (a) whether the original regulatory method was "adequate and practicable for regulatory purposes" and (b) whether there were any other "adequate and reliable methods" that were "practicable for regulatory purposes and capable of detecting and identifying residues in edible tissues 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." *Diethylstilbestrol; Notice of Hearing on Proposal to Withdraw Approval of New Animal Drug Applications*, 41 Fed. Reg. 52,105, 52,106 (Nov. 26, 1976).

59. The DES sponsors were then provided a *formal* evidentiary hearing in accordance with 21 U.S.C. § 360b(e)(1) and FDA's Part 12 regulations. *See Diethylstilbestrol; Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision*, 44 Fed. Reg. 54,852, 54,852 (Sept. 21, 1979). For example, the hearing was held before an administrative law judge and included an opportunity for the drug sponsor to cross-examine adverse witnesses. *See id. After* affording the sponsors a meaningful opportunity to be heard, FDA revoked the DES regulatory method and withdrew the NADA approvals that depended on that method. *Id.* FDA's order explained that the approved method of detecting DES residues was not adequate for regulatory purposes, and that there were no other adequate and reliable methods that could meet the statutory requirements of the DES Proviso. *Id.* FDA further reasoned that, once there is no longer an approved regulatory method in place, the FDCA "then *compels* [FDA] to withdraw all NADA approvals that were based on compliance with [the withdrawn method] because . . . the

Delaney Claus[e] becomes applicable to the drug." *Id.* at 54,859 (emphasis added); *see also id.* at 54,900 ("Because I have revoked approval of the analytical method for detecting DES residues and have not substituted for it any other approved method . . . [t]he Delaney Clause, therefore, applies to DES and . . . requires withdrawal of approval of all DES NADA[s].").[4]

60. Following the DES proceedings, FDA withdrew approvals for a class of chemicals known as "nitrofurans." *See Nitrofurans; Withdrawal of New Animal Drug Applications*, 56 Fed. Reg. 41,902, 41,902 (Aug. 23, 1991). FDA issued a NOOH and then provided the nitrofurans sponsors a formal evidentiary hearing that addressed whether the Delaney Clause applied (nitrofurans previously had not been considered carcinogenic), and whether an adequate regulatory method triggered the DES Proviso. *See id.* at 41,904–11. As with the DES precedent, FDA followed the proper statutory process in withdrawing the nitrofurans approvals by holding an evidentiary hearing to consider the applicability of the Delaney Clause and DES Proviso—including the existence of any valid, regulatory method. *See* 21 U.S.C. § 360b(e)(1)(B), (d)(1)(I). As these proceedings show, for drugs potentially subject to disapproval under the Delaney Clause, the regulatory method for a drug is inextricably linked with proceedings regarding disapproval of the drug.

c) <u>FDA Citizen Petitions</u>

61. FDA regulations provide that an interested person "may petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action." 21 C.F.R. § 10.25(a).

[4] At the time of FDA's September 1979 order, the Delaney Clause was codified at 21 U.S.C. § 360b(d)(1)(H); due to intervening amendments, that provision is now codified at § 360b(d)(1)(I).

II. Judicial Review Under the Administrative Procedure Act

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

63. Under the APA, a court must "hold unlawful and set aside agency action . . . found to be . . . arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law," "contrary to constitutional right," "in excess of statutory jurisdiction, authority, or limitations," or "without observance of [the] procedure required by law." *Id.* § 706(2)(A)–(D).

64. Agency action is arbitrary and capricious if, among other things, "the agency has relied on factors which Congress has not intended it to consider, entirely failed to consider an important aspect of the problem, offered an explanation for its decision that runs counter to the evidence before the agency, or is so implausible that it could not be ascribed to a difference in view or the product of agency expertise." *Motor Vehicle Mfrs. Assoc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). An agency likewise violates the APA if it departs without reasoned explanation from past agency practice, *see FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515–16 (2009), or when the agency fails "to give a reasoned explanation for its rejection of [proposed] alternatives," *Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 242 (D.C. Cir. 2008); *see also Del. Dep't of Nat. Res. & Envtl. Control v. EPA*, 785 F.3d 1, 11 (D.C. Cir. 2015).

FACTUAL BACKGROUND

I. Carbadox Provides a Safe, Effective, and Irreplaceable Means of Treating Serious Diseases in Pigs.

65. FDA first approved carbadox in 1972 under New Animal Drug Application 041-061, concluding that carbadox is a safe and effective means of controlling dysentery and bacterial swine enteritis, among other indications. *See Tolerances for Residues of New Animal Drugs in Food; Carbadox*, 37 Fed. Reg. 20,683–85 (Oct. 3, 1972).

66. Swine dysentery and bacterial swine enteritis are debilitating diseases for newborn pigs, and they pose serious threats to the U.S. swine industry. Both diseases can be fatal if untreated, and pigs suffering from these diseases may experience bloody diarrhea, dehydration, and weight loss.

67. Untreated swine dysentery spreads rapidly, with infected pigs and contaminated waste known to cause outbreaks that can decimate hundreds or even thousands of pigs at a single location.

68. Carbadox is especially important to confronting swine dysentery and controlling bacterial enteritis because, despite a half century of use in the marketplace, it shows little, if any, development of antimicrobial resistance. *See* FDA, *Questions and Answers Regarding Carbadox*, https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox (accessed Jan. 4, 2024) ("While carbadox is also an antimicrobial, it does not pose the same resistance issues as other antimicrobials and is not considered important to human medicine.") (attached as **Exhibit 1**). Partly because of this characteristic, it is estimated that removing carbadox from the market would cost the U.S. swine industry $5.3 billion dollars over ten years.

69. Carbadox has been in widespread use by pork producers throughout the half century since it was approved. Today, pork producers treat more than 35 million pigs with carbadox each year, representing approximately 65 percent of all pigs raised in the United States.

70. Most pigs are raised for six months before they are sent to market to be slaughtered. *See, e.g.*, National Pork Board, *Life Cycle of a Market Pig*, https://porkcheckoff.org/pork-branding/facts-statistics/life-cycle-of-a-market-pig/ (accessed Jan. 4, 2024). With respect to that six-month lifespan, most pigs are treated with carbadox shortly after they are born, between three

weeks and eleven weeks of age. The drug is combined with feed and usually administered for a period of 42 to 56 days. In most instances, pigs are not treated with carbadox after they reach ten to twelve weeks old—meaning that 100 to 120 days typically elapse between the last administration of carbadox and the date when the pig is sent to market.

71. Carbadox and its metabolite desoxycarbadox are potential carcinogens under laboratory conditions. However, after the pig ingests carbadox, both carbadox and desoxycarbadox soon degrade to quinoxaline-2-carboylic acid ("QCA"), a harmless substance.

72. It has long been understood that when a pig ingests carbadox, the drug first metabolizes to desoxycarbadox, which then degrades to QCA. An April 2022 study (the "Zhang study") presented evidence that there may be an alternative pathway whereby carbadox first loses the portion of the molecule that makes it carcinogenic, and is then metabolized into QCA without ever turning into desoxycarbadox or any other carcinogenic molecule. In the pig's body, both of these degradation reactions can go in only one direction (i.e., QCA cannot regenerate desoxycarbadox or carbadox, and desoxycarbadox cannot regenerate carbadox). FDA acknowledged as much in 1998, and subsequently has not called that conclusion into question. *See* FDA, Corrected Freedom of Information Summary, Supplement to NADA 041-061, Mecadox® 10 (carbadox) Type A medicated article, supplemental approval, at 9 (Jan. 30, 1998) ("FOI Summary"), *available at* https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/308 ("the *in vivo* metabolism of the compounds of carcinogenic concern is . . . irreversible such that the resulting metabolic products cannot regenerate compounds of carcinogenic concerns").

73. During this metabolic process, other chemical compounds may form fleetingly and decay rapidly. For example, when a desoxycarbadox molecule converts into a QCA molecule, a

third molecule called hydrazine can also be produced. Likewise, the Zhang study postulated an alternative chemical pathway by which carbadox decays to QCA not via desoxycarbadox but instead via a small number of short-lived intermediate compounds. Crucially, however, to the extent any of these short-lived metabolites can even be detected and measured, they have been found to decay rapidly: the Zhang study showed that some intermediates could not be detected at all, while the others fell below the study's limit of detection by 24 hours after dosing.

74. Studies show that carbadox becomes undetectable at or above one part per billion in swine liver tissue between zero and seven days after dosing, and based on data from those studies, desoxycarbadox is calculated to become undetectable in liver tissue at or above 0.915 parts per billion—the S_m, or safe level determined by FDA—by approximately 26 days after dosing. The liver is the tissue in which it takes the longest for carbadox and desoxycarbadox to deplete, such that when those substances cannot be detected in the liver, they will not be found anywhere else in the pig's body.

75. Relying on similar data, FDA's 1972 approval decision concluded that carbadox can be used in a manner that does not pose health risks to animals or humans, and therefore meets the criteria of the DES Proviso. *See* 21 C.F.R. § 135g.81 (1972); *Tolerances for Residues of New Animal Drugs in Food; Carbadox*, 37 Fed. Reg. 20,683, 20,683–85 (Oct. 3, 1972). The approval decision prescribed a 70-day withdrawal period for carbadox, as well as a regulatory method for measuring the level of carbadox residues in pork products from pigs treated with carbadox. *See* 21 C.F.R. § 135g.81 (1972).

76. Phibro is not aware of even a single instance of carbadox causing cancer in pigs or in humans in the half-century in which it has been used, and FDA has not put forth any such evidence.

II. FDA Has Repeatedly Approved Supplemental Carbadox Applications Since 1972.

77. In 1975, FDA again approved a form of carbadox—a combination of carbadox and pyrantel tartrate—under NADA 092-955. In addition to the indications for carbadox approved in 1972, the new combination drug was indicated for prevention of the migration and establishment of large roundworm infections and the establishment of nodular worm infections. *See New Animal Drugs for Use in Animal Feeds; Carbadox, Pyrantel Tartrate*, 40 Fed. Reg. 45,164, 45,164–65 (Oct. 1, 1975). FDA prescribed a 70-day withdrawal period for this combination drug.

78. In January 1998, FDA once again approved a supplemental carbadox application, NADA 041-061. The supplemental application presented additional data about the potentially carcinogenic effects of carbadox and desoxycarbadox at high doses in laboratory animals. The new data confirmed that QCA is a harmless molecule, including in laboratory animals. Accordingly, FDA approved the supplemental application, finding that, although carbadox and desoxycarbadox have carcinogenic effects at high doses in laboratory conditions, it is possible to set a safe level for these residues in the human diet and, therefore, in the edible tissues of food animals. *See Tolerances for Residues of New Animal Drugs in Food; Carbadox*, 63 Fed. Reg. 13,337, 13,337 (Mar. 19, 1998).

79. As part of the January 1998 supplemental NADA approval, FDA took three steps regarding carbadox's regulatory method. *First*, FDA determined that neither carbadox nor desoxycarbadox was detectible after 72 hours post-dosing and that all nonextractable carbadox residues were noncarcinogenic and related to the harmless metabolite QCA. *See* FOI Summary at 9. *Second*, FDA "removed" the original regulatory method approved in 1972 from the Code of Federal Regulations, concluding that "better and more accurate regulatory procedures" were available "in general use." 63 Fed. Reg. at 13,337. *Third*, FDA adopted a new regulatory method for carbadox by setting "a finite tolerance" of 30 parts per billion (ppb) for QCA in swine liver

and codified this tolerance level in the Code of Federal Regulations. *Id.*; *see* 21 C.F.R. § 556.100 (1998). FDA retained the 70-day withdrawal period for carbadox originally set in 1972, on the understanding that carbadox and desoxycarbadox would be "well below" safe levels at the time of slaughter. *See* FOI Summary at 14.

80. In selecting the tolerance level, FDA evaluated studies demonstrating the carcinogenicity of carbadox and desoxycarbadox and establishing that desoxycarbadox was the most potent of these compounds. Based on desoxycarbadox, FDA calculated an S_o of 0.061 ppb for total carbadox residues of carcinogenic concern in the human diet. *Id.* FDA then calculated an S_m value for total residues of carcinogenic concern in muscle at 0.305 ppb, in liver at .915 ppb, and in kidney and fat at 1.830 ppb. *Id.* Because FDA concluded that carbadox was rapidly metabolized (i.e., carcinogenic residues were not detectable soon after dosing), it did not establish an R_m value. Instead, FDA established QCA as the assigned marker residue because it was the only metabolite known to be detectable after 72 hours post-dosing. *Id.*

81. FDA codified only a portion of the new tolerance-based method it approved in January 1998. *See* 63 Fed. Reg. at 13,337. It included the remaining details in a separate Freedom of Information document. *See* FOI Summary at 13–14.

82. In October 1998, FDA approved a supplemental application that shortened the withdrawal period from 70 to 42 days for carbadox under NADA 041-061. *See New Animal Drugs for Use in Animal Feeds; Carbadox*, 63 Fed. Reg. 59,216, 59,216 (Nov. 3, 1998). The withdrawal period for the combination drug formed with carbadox and pytrantel tartrate, which had been approved under NADA 092-955, remained at 70 days.

83. In 2004, FDA approved under NADA 141-211 a combination of carbadox and oxytetracycline dihydrate base. That combination was approved, among other indications, to treat

bacterial enteritis caused by *E. coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, and to treat bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline. 69 Fed. Reg. 51,173, 51,173 (Aug. 18, 2004); 21 C.F.R. § 558.450 (2004). The withdrawal period for this combination drug is 42 days.

84. All of the NADA approvals recited above remain in effect as of the date on which this lawsuit is filed, and all of the drugs corresponding to those approvals remain on the market and in use by pork producers.

III. CVM Reverses Course by Requiring Data on Chemically Inert, "Bound" Residues in Swine Treated with Carbadox.

85. CVM is the FDA component organization responsible for regulating animal drugs and in that capacity reviewed and approved the carbadox NADAs described in paragraphs 65 to 84 above.

86. In evaluating and approving the NADAs for carbadox and new carbadox combination products through 2004, CVM took the scientifically appropriate position that "bound" residues—that is, residues attached to the structure of animal proteins that are otherwise inert—are not of carcinogenic concern. CVM historically had no concerns about the fact that laboratories could not extract bound carbadox residues from liver tissue collected at the end of the 42-day withdrawal period because all the residue molecules remaining in the pig had by that point become bound to the pig's structural proteins, were chemically inert, and were not carcinogens.

87. CVM shifted the goalposts when, in December 2011 and March 2012, it informed Phibro, for the first time, that *all* carbadox residues—including theoretical metabolites of carbadox that had been converted to harmless QCA but could not be extracted because they were bound to animal tissues—would now be presumed to be "of carcinogenic concern" unless they are shown

not to be carcinogenic. Previously, CVM had taken the position that "the unextractable residues are related to non-carcinogenic compounds," such as QCA. FOI Summary at 9.

88. To meet CVM's new requirement, Phibro would need to prove that 100% of carbadox residues—including the chemically inert residue bound to the animal's tissues that scientists were not then able to extract and that FDA had always considered unavailable to (and thus not a health risk for) persons ingesting the tissue—were not of carcinogenic concern. CVM had never before required a drug sponsor to make such a showing, yet imposed this requirement on Phibro.

89. Working for the next several years with independent expert laboratories, Phibro compiled what CVM demanded: data showing that the bound carbadox residues posed no health risk. The study results showed that no carcinogenic residues could be detected in pig liver at the end of the withdrawal period. Although some harmless QCA remained at low levels, the data showed that neither carbadox nor desoxycarbadox remained present above 1 ppb by 21 days after dosing. In particular, a pilot study detected no carbadox, desoxycarbadox, or QCA on days 21 or 40 of the 42-day withdrawal period.

IV. CVM Issues Its 2016 Notice of Opportunity for Hearing and Agrees That Phibro is Entitled to a Hearing.

90. On April 12, 2016, on the eve of Phibro submitting the results of the multi-year scientific effort reconfirming the safety of carbadox, which CVM knew was coming, FDA shifted the goalposts a second time. CVM issued a Notice of Opportunity for Hearing (the "2016 NOOH") informing Phibro that CVM proposed to withdraw approvals for all of the carbadox NADAs. *See Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Opportunity for Hearin*g, 81 Fed. Reg. 21,559, 21,559–73 (Apr. 12, 2016). The 2016 NOOH required Phibro to request a hearing "[i]n accordance with" the provisions that govern formal, evidentiary hearings under the

FDA's rules. *Id.* at 21,572 (citing 21 C.F.R. parts 12 & 514). Recall that the FDCA and FDA's own regulations mandate that the agency must provide the sponsor of an approved drug an opportunity for a formal evidentiary hearing before withdrawing the drug from the market. *See, e.g.*, 21 U.S.C. § 360b(e)(1).

91. CVM argued in the 2016 NOOH that withdrawal of the carbadox NADA approvals—and thus removal of carbadox from the market—was warranted because (a) carbadox no longer met applicable safety requirements in light of additional data, and (b) the approved regulatory method was insufficient to confirm that no carcinogenic residue remained in edible portions of pigs at the time of slaughter. *See* 81 Fed. Reg. at 21,561. The 2016 NOOH mentioned bound residues in passing, but did not cite concerns about those residues as a reason warranting withdrawal of the carbadox NADA approvals.

92. On April 14, 2016, Phibro requested a hearing and on July 11, 2016, Phibro responded to the 2016 NOOH by providing detailed data generated when Phibro successfully extracted and characterized all carbadox residues in the animal, including those that had become bound to the animal's tissues and so had been difficult or impossible to extract previously. Those detailed data showed (a) the rapid depletion of potentially carcinogenic residues in edible tissues so that by the time the animal is slaughtered, no residues FDA had deemed to be unsafe are detectable and (b) the appropriateness of QCA as a marker residue. Together, these submissions demonstrated that carbadox is safe and effective when administered according to its labeling, and that there was therefore no basis for CVM's proposal to withdraw the carbadox NADA approvals.

93. Between July 2016 and July 2020, Phibro responded to nearly 200 follow-up inquiries from CVM about these issues.

94. On April 17, 2017, then-CVM Director Steven Solomon acknowledged that an evidentiary hearing was warranted and therefore recommended that FDA grant Phibro's hearing request in substantial part. *See* 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 11 (Apr. 17, 2017), *available at* https://www.regulations.gov/document/FDA-2016-N-0832-0052.

95. The Office of Scientific Integrity within the FDA Office of the Commissioner responded to CVM's recommendation on October 30, 2017. The Office of the Commissioner first noted CVM's acknowledgement "that Phibro's request for a hearing, as supplemented by data, information, and analysis, has created genuine and substantial issues of fact with respect to CVM's proposed withdrawal of carbadox and that, therefore, Phibro has justified a hearing under 21 CFR 12.24(b)"—i.e., a formal evidentiary hearing under Part 12 of FDA's regulations. Docket No. FDA-2016-N-0832, Doc. No. 0055, *Re: Docket No. FDA-2016-N-0832; Carbadox*, at 2 (Oct. 30, 2017), *available at* https://www.regulations.gov/document/FDA-2016-N-0832-0055; *see* ¶¶ 51–52, *supra*. The October 30, 2017 memorandum then directed CVM to provide within 60 days a scientific analysis of Phibro's studies to help narrow the scientific and factual issues to those on which CVM and Phibro did not agree. *See* Docket No. FDA-2016-N-0832, Doc. No. 0055, *Re: Docket No. FDA-2016-N-0832; Carbadox*, at 3.

96. CVM sought and obtained multiple extensions of that 60-day deadline, and on March 16, 2018 requested an "indefinite stay" of the deadline "to allow it to receive and fully analyze all of the data and analyses Phibro plans to submit to [CVM] and to take appropriate action in response." Docket No. FDA-2016-N-0832, Doc. No. 0058, *Re: Docket No. FDA-2016-N-0832; Carbadox*, at 1 (Mar. 16, 2018), *available at* https://www.regulations.gov/document/FDA-2016-

N-0832-0058. CVM added that an indefinite stay would aid the agency in "evaluat[ing] and consider[ing] a variety of options for how best to proceed," including "withdrawing the" 2016 NOOH, "working cooperatively with Phibro to develop or gather additional information related to carbadox," and "amending, revising, or reissuing the [2016] NOOH." *Id.* at 2. The Office of the Commissioner granted the stay on March 30, 2018. *See* Docket No. FDA-2016-N-0832, Doc. No. 0060, *Re: Docket No. FDA-2016-N-0832; Carbadox*, at 1 (Mar. 30, 2018), *available at* https://www.regulations.gov/document/FDA-2016-N-0832-0060. CVM eventually provided the analysis mandated by the Office of the Commissioner's October 30, 2017 memorandum nearly three years later on July 15, 2020.

97. Despite the consensus that Phibro was entitled to a hearing, FDA never scheduled or conducted a hearing regarding the issues presented by the 2016 NOOH.

V. CVM Withdraws the 2016 NOOH and Initiates a New Proceeding to Revoke Approval for the Carbadox Regulatory Method.

98. On July 20, 2020, CVM shifted course a third time. Rather than proceeding with a formal evidentiary hearing on the allegations in its 2016 NOOH, as it had agreed to, CVM (a) issued a notice withdrawing the 2016 NOOH, and (b) published a new proposed declaratory order, which, if finalized, would revoke the approved carbadox regulatory method. *See Phibro Animal Health Corp.: Carbadox in Medicated Swine Feed; Withdrawal of Notice of Opportunity for Hearing*, 85 Fed. Reg. 43,852, 43,852–53 (July 20, 2020); *Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method*, 85 Fed. Reg. 43,853, 43,853–58 (July 20, 2020) (the "2020 Proposed Order").

99. The 2020 Proposed Order did not challenge the safety or efficacy of carbadox. Instead, it asserted that the approved regulatory method, adopted in 1998, must be revoked "because there is no established relationship between QCA measured by the approved method and

the residue of carcinogenic concern," such that the method does not "compl[y] with FDA's operational definition of no residue." 85 Fed. Reg. at 43,853.

100. The 2020 Proposed Order acknowledged that in 1998, CVM "did not require the sponsor to provide data showing the relationship between QCA and the residue of carcinogenic concern"—and therefore did not establish an R_m value for QCA. *Id.* at 43,858; *see also* 63 Fed. Reg. at 13,337. An R_m would have established the level of QCA residue that reflects safe (i.e., S_m) levels of carbadox and desoxycarbadox residues in pork products. Instead, CVM's 1998 decision established a finite "tolerance of 30 ppb [parts per billion] for QCA in swine liver" because, as CVM publicly stated, it believed that "a tolerance would adequately protect public health." 85 Fed. Reg. at 43,855–56. CVM explained at the time that "no residues of carcinogenic concern remain in the carcass when using an assigned value of 30 ppb for the noncarcinogenic market residue (QCA)." FOI Summary at 14. The 2020 Proposed Order departed from those conclusions, asserting that "[w]ithout an R_m and an appropriate regulatory method for detecting when the marker residue falls below the R_m, it is impossible to determine that the residue of carcinogenic concern falls below" safe levels. 85 Fed. Reg. at 43,858.

101. The Proposed Order also asserted, purportedly based on "new data," that carbadox residues do not deplete "as quickly as previously believed," thus "underscor[ing]" in CVM's view the "importance of addressing the inadequacies of the current approved [regulatory] method." *Id.* at 43,854.

102. CVM further stated that, upon finalizing the 2020 Proposed Order, CVM "intend[ed] to publish in the Federal Register a notice of opportunity for hearing (NOOH) proposing to withdraw all new animal drug applications for use of carbadox based on the lack of an approved [regulatory] method." *Id.* This new proceeding would be based on the fact that there

would no longer be an approved regulatory method for the drug: In the absence of an approved method, the DES Proviso would no longer apply and withdrawal of the carbadox NADA approvals would be required under the Delaney Clause, 21 U.S.C. § 360b(d)(1)(I), and the corresponding withdrawal provision, 21 U.S.C. § 360b(e)(1). *See* 85 Fed. Reg. at 43,855; *see also* ¶ 48, *supra*.

103. A CVM spokesperson, Veronika Pfaeffle, explained the agency's rationale in an interview with *Bloomberg News*, stating that "going after the testing method . . . 'is the most straightforward and least resource-intensive process for removing carbadox from the market.'" Anna Edney, *Why Is a Drug Banned in Europe, Canada Still Being Fed to U.S. Pork?*, Bloomberg News (Mar. 3, 2022), *available at* https://www.bloomberg.com/news/articles/2022-03-03/stalemate-at-fda-puts-pork-with-toxic-risk-in-u-s-food-supply (attached as **Exhibit 2**). That public statement mirrored internal CVM correspondence—obtained by Phibro under the Freedom of Information Act—in which agency officials stated that "CVM [has] decided that the most straightforward and expeditious way to remove carbadox from the market is to revoke the approved regulatory method for carbadox." FDA, *Questions and Answers Regarding Carbadox*, at 3 (Dec. 9, 2019 draft) (attached as **Exhibit 3**).

104. Public statements on FDA's website further underscore that the agency predetermined the outcome of proceedings on the 2020 Proposed Order. In July 2019, FDA posted a document titled *Questions and Answers Regarding Carbadox* on its website, explaining at the time that CVM "want[s] to remove carbadox from the market" and was "working to have carbadox removed from the market." FDA, *Questions and Answers Regarding Carbadox*, at 2 (July 31, 2019 archive) (attached as **Exhibit 4**). FDA updated this document several times during the proceedings on the 2020 Proposed Order, each time including language stating that "CVM is working to remove the drug from the market." *See, e.g.*, FDA, *Questions and Answers Regarding*

Carbadox, at 3 (July 17, 2020 archive) (attached as **Exhibit 5**).[5] That language remains on FDA's website today. *See* FDA, *Questions and Answers Regarding Carbadox*, https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox (accessed Jan. 4, 2024).

105. Under FDA precedent—including the agency's 1979 order rescinding marketing authorization (after a formal evidentiary hearing) for DES, *see* ¶ 59, *supra*—an order revoking the carbadox regulatory method eliminates a necessary condition to maintain approval for the carbadox NADAs and thus obligates the agency to take the further step of removing carbadox from the market. *See, e.g.*, 44 Fed. Reg. at 54,860 (FDA is "require[d]" to withdraw "approval of" the NADAs for an approved but potentially carcinogenic drug if there is no longer an approved regulatory method for the drug); *see also id.* at 54,900 (applying that principle). Moreover, revoking approval for the carbadox regulatory method through a declaratory order would take questions regarding the method's validity (and the validity of Phibro's proposed alternative methods) off the table in any future NADA withdrawal hearing. The 2020 Proposed Order thus sought to withdraw the carbadox regulatory method as a back-door means of revoking the carbadox NADA approvals, *without* holding the formal evidentiary hearing that otherwise would be required under 21 U.S.C. § 360b(e) before taking an approved drug off the market.

VI. Phibro's Response to the 2020 Proposed Order

106. In September 2020, Phibro timely submitted a detailed, 93-page response to the 2020 Proposed Order—along with 53 exhibits, totaling 3,543 pages. The comment letter, a copy

[5] Additional archived copies of the *Questions and Answers Regarding Carbadox* webpage are available from the Internet Archive by entering "https://www.fda.gov/animal-veterinary/product-safety-information/questions-and-answers-regarding-carbadox" in the search field at https://web.archive.org/.

of which is attached as **Exhibit 6**, shows that the governing statutory and regulatory framework entitles Phibro to a hearing conducted by an impartial adjudicator *before* CVM withdraws approval of the carbadox NADAs or the regulatory method supporting those approvals. *See* **Exhibit 6** at 34–44 (citing 21 U.S.C. § 360b(e)(1) and 21 C.F.R. §§ 10.55(b)(2)(i), 514.201). Because approval of the regulatory method is inextricably intertwined with approval of carbadox itself, and because withdrawal of the method inexorably leads to withdrawal of the NADA approvals under longstanding agency precedent, Phibro argued that CVM must consider those issues together in a single proceeding.

107. Phibro's response also explained that the 2020 Proposed Order was arbitrary and capricious. In particular, Phibro presented extensive evidence and expert testimony showing that (a) the regulatory method approved in 1998 remains appropriate and fully consistent with applicable law, and (b) alternative regulatory methods—including protocols employed by the U.S. Department of Agriculture and the Canadian Food Inspection Agency—are available even if the 1998 method is withdrawn. *See* **Exhibit 6** at 46–49, 60–77, 78–81. Phibro's evidence included a 2020 CVM memorandum acknowledging that the Canadian method "has been used successfully for many years." A true and correct copy of this memorandum, which Phibro obtained through the Freedom of Information Act, is attached as **Exhibit 7**.

108. Other parties also responded in opposition to the 2020 Proposed Order. The American Association of Swine Veterinarians submitted comments regarding the negative health effects that would result if carbadox were removed from the market. The Association expressed concern that if carbadox were not available, more pigs would die from enteric disease, such as dysentery and salmonellosis. Removal of carbadox would also inevitably increase use of other antibiotics, resulting in increased antimicrobial resistance for those classes of drugs. That result,

the Association explained, would conflict with a major Department of Health and Human Services initiative to decrease antimicrobial resistance for drugs that are important to human medicine. Therefore, the Association requested that FDA work with Phibro to develop and approve a new regulatory method rather than remove carbadox from the market.

109. The National Pork Producers Council likewise submitted comments expressing concerns about the economic impact of removing carbadox from the market, as well as concerns about antimicrobial resistance that would likely result from the drugs used as substitutes for carbadox. Among other things, the Council estimated that removing carbadox from the market would inflict up to $500 million in losses to the U.S. pork production industry in the first year, driven by the higher level of disease and death losses, and that the cost to the industry over the next ten years could reach $5.3 billion.

110. In November 2020, Phibro supplemented its response to the 2020 Proposed Order by submitting a citizen petition pursuant to 21 C.F.R. § 10.30 and 21 C.F.R. § 10.35. The petition, a copy of which is attached as **Exhibit 8**, requested that FDA refrain from finalizing, and withdraw, the 2020 Proposed Order, thereby allowing for consideration of the carbadox regulatory method and NADA approvals together in a single, combined proceeding—consistent with applicable law and FDA precedent (including the DES proceeding).

111. Phibro provided additional arguments and evidence in the citizen petition and related filings in support of the positions taken in Phibro's response to the 2020 Proposed Order. In particular, Phibro reiterated that (a) carbadox is safe and effective; (b) FDA lacks authority to revoke the regulatory method in a standalone proceeding; (c) the Proposed Order departs from FDA precedent (including the DES proceeding) without an adequate justification; and (d) both the regulatory method approved in 1998 and the Canadian and USDA methods satisfy all applicable

legal requirements. In addition, the petition showed that the 2020 Proposed Order would destabilize the market for carbadox products and the swine industry more broadly—for example by calling into question whether pork products derived from pigs treated with carbadox may be lawfully sold in the absence of an approved regulatory method.

112. Finally, the citizen petition explained that removing carbadox from the market would create serious antimicrobial resistance concerns. The Department of Health and Human Services has determined that antimicrobial resistance—the ability of a microorganism to resist the effects of a drug—presents a growing public-health threat. Antimicrobial resistance occurs when drugs used in animals are also used to treat infections in humans. Carbadox is not used to treat human infections and therefore does not contribute to antimicrobial resistance. Critically, however, if carbadox were removed from the market, pork producers would be forced to switch to alternative products that do create concerns about antimicrobial resistance (because unlike carbadox, those classes of drugs are used as antibiotics in humans and swine).

VII. FDA Responds and Holds an Informal Public Meeting Under Part 15 of the Agency's Regulations.

113. FDA did not take further substantive action on the matter for more than a year. On January 6, 2022, CVM issued a written response to Phibro's objections. *See CVM Response to Phibro Animal Health Corporation's September 18, 2020 Comments on CVM's July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox* (Jan. 6, 2022), *available at* https://www.regulations.gov/document/FDA-2021-N-1326-0004. In that response, CVM primarily claimed that Phibro had not provided sufficient data to establish the safe concentration level for QCA, the marker residue used for the approved carbadox regulatory method. *See id.* at 2–3. CVM also maintained that there was insufficient data to support the alternative Canadian Food Inspection Agency methodology. *Id.*

114. One week later, FDA announced that it would hold an "informal" public meeting under Part 15 of FDA's regulations to gather data on various topics related to carbadox. *See Scientific Data and Information Related to the Residue of Carcinogenic Concern for the New Animal Drug Carbadox; Public Hearing; Request for Comments*, 87 Fed. Reg. 2,093, 2,094 (Jan. 13, 2022). FDA held the public meeting on March 10, 2022. In accordance with Part 15's relaxed procedures, no "rules of evidence" applied to the hearing, and Phibro was not permitted to cross-examine witnesses. *Id.* Instead, "[o]nly the presiding officer and panel members" were authorized to "pose questions." *Id.* Members of the public were invited to participate and present their views. *Id.* at 2,095.

115. The panel of FDA officials who conducted this informal public meeting lacked independent authority to take binding regulatory action regarding the carbadox regulatory method or approval of the carbadox NADAs. Indeed, the panel lacked authority to resolve any disputed issue regarding those issues, either in favor of Phibro or CVM. FDA personnel acknowledged as much in internal correspondence, stating that the public meeting would involve "no debates," "no opin[i]ons," and "no conclusions," Mar. 7, 2022 Messages Between Jonathan Greene and Julia Oriani, at 4 (attached as **Exhibit 9**)—making the meeting "a big waste of time," Jan. 24, 2022 Messages Between Kimon Kanelakis and Jonathan Greene, at 7 (attached as **Exhibit 10**). Given these limitations, the public meeting served a fundamentally different purpose than a formal evidentiary hearing under FDA's Part 12 rules, as required by 21 U.S.C. § 360b(e) and related provisions.

116. The Part 15 meeting also lacked many of the procedural protections that apply to Part 12 hearings, and that are required by law for determination of factual issues central to whether a NADA approval will be withdrawn. For example:

a. Contrary to the separation-of-function requirements that govern Part 12 hearings, *see* 21 U.S.C. § 360b(e)(1); 21 C.F.R. §§ 12.60, 10.55(b)(2)(i), the panel that presided over the Part 15 meeting was not impartial because it was partly comprised of representatives from CVM, the FDA component seeking to revoke the regulatory method for carbadox.

b. The panel members were not "adjudicators" because they lacked authority to issue a ruling on the adequacy of the approved carbadox regulatory method. *Cf. id.* § 12.120 (outlining requirements for written decision following Part 12 evidentiary hearing).

c. Even though the panel members could ask questions of the witnesses, Phibro could not. *Cf. id.* §§ 12.70(b), 12.87(b)(1)(ii), 12.89(b)(2), 12.94(d) (right to cross-examine witnesses in Part 12 hearing).

d. The panel permitted a wide range of third parties to comment on issues relating to carbadox, but did not screen those comments for relevance, require them to be based on admissible evidence, or permit Phibro's representatives to question the third-party speakers. *See, e.g.*, Transcript of March 10 Meeting ("March 2022 H'rg Tr.") at 43–57, *available at* https://downloads.regulations.gov/FDA-2021-N-1326-1567/attachment_1.pdf.

e. Documents obtained through the Freedom of Information Act show that one of the panelists who participated in the meeting advised CVM's witness on strategy for the meeting and provided advance comments on the content of the CVM witness's presentation.[6] The officials acknowledged that they "shouldn[']t discuss" these issues

[6] Specifically, on January 7, 2022, Dr. Julia Oriani (CVM's lead presenter) asked Dr. Jonathan Greene (a CVM panelist) to review her slides for the upcoming public meeting. *See* Jan. 7, 2022 (continued…)

with each other, but did so anyway, **Exhibit 9** at 4, and later exchanged e-mails about an unpublished carbadox study that the CVM witness was "not even supposed to say anything" about. **Exhibit 13** at 30; *see also* **Exhibit 13** at 27 (boasting that "Phibro doesn't know about [the new study] ha ha"). In additional correspondence, one of these officials told another that during the hearing she "kept off [Microsoft] teams in case that was better documentation wise 😉," suggesting that the sender may have deliberately sought to conceal her communications. Mar. 10, 2022 Message from Holly Erdely to Jonathan Greene, at 1 (attached as **Exhibit 21**).

f. Internal correspondence likewise reveals that FDA officials "kept sending" each other Internet memes "when pah [an apparent reference to Phibro Animal Health] w[as] speakin[g]" and that the officials found it "exhausting" to sit through Phibro's presentation. Mar. 11, 2022 Messages Between Kimon Kanelakis and Jonathan Greene, at 33, 51 (attached as **Exhibit 15**). These memes included the following image, apparently intended to mock Phibro's arguments:

Message from Julia Oriani to Jonathan Greene, at 1 (attached as **Exhibit 11**). That same day, Oriani asked Greene to participate in a practice session for her carbadox presentation. *See* Jan. 7 & 10, 2022 Messages Between Julia Oriani and Jonathan Greene, at 1 (attached as **Exhibit 12**). On January 10, Oriani and Greene discussed feedback on Oriani's presentation. *See id.* at 9–17, 20–21. On January 12, Greene helped Oriani make formatting changes to her slides based on feedback from the FDA Office of the Chief Counsel. *See* Jan. 12, 2022 Messages Between Julia Oriani and Jonathan Greene, at 1–18 (attached as **Exhibit 13**). And on January 14, Oriani asked Greene to review her revised slides. *See* Jan. 14, 2022 Message from Julia Oriani to Jonathan Greene, at 1 (attached as **Exhibit 14**).

Id. at 32.

117. During the public meeting, Phibro raised its procedural concerns. It explained that the meeting lacked critical "protections" like an impartial adjudicator and the right to cross-examine witnesses. Mar. 2022 H'rg Tr. at 44. In response, the FDA panel chair ended Phibro's portion of the meeting and called for a "5-minute break." *Id.*

118. Despite these procedural impediments, Phibro gave a detailed presentation at the public meeting showing that carbadox is safe and that removing the drug from the market would cause significant harm. *See* Mar. 2022 H'rg Tr. at 10–44; *see also* Slide Presentation by Phibro Animal Health Corporation to FDA (Mar. 10, 2022) (attached as **Exhibit 16**).

119. For example, Phibro discussed studies confirming that there are no detectable carbadox residues of carcinogenic concern at the end of the mandated 42-day withdrawal period. *See* Mar. 2022 H'rg Tr. at 15–18, 23–27. The studies showed that the only detectable residue following that period is QCA that is bound to structural proteins, and therefore completely inert. *Id.* at 15, 23.

120. Phibro's presentation also described the substantial harms that would result if carbadox were removed from the market, including more than 4 million additional pig deaths per year; approximately $5.3 billion in cost to the swine industry over ten years; and an increased risk of resistance to antibiotics used in humans. *Id.* at 11.

121. After the public meeting, Phibro supplemented its presentation with three written submissions.

122. *First*, Phibro submitted a letter explaining that the informal public meeting was not an adequate substitute for the formal evidentiary hearing required under Part 12 of FDA's regulations—and mandated by the Fifth Amendment's Due Process Clause, the APA, and the FDCA. *See Phibro Animal Health Corporation Comment Regarding Due Process Issues* (June 9, 2022), *available at* https://www.regulations.gov/comment/FDA-2021-N-1326-2212.

123. *Second*, Phibro replied to FDA's January 2022 response to Phibro's comments on the 2020 Proposed Revocation Order. *See Phibro Reply to the January 6, 2022 CVM Response to Phibro Animal Health Corporation's September 18, 2020 Comments on CVM's July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox* (June 9, 2022), *available at* https://www.regulations.gov/comment/FDA-2021-N-1326-2214. Phibro's reply explained that, contrary to CVM's claims, the agency had at its disposal the data necessary to calculate a safe

concentration level for QCA as a marker residue for carbadox, and that sufficient data supported the alternative Canadian Food Inspection Agency methodology. *Id.* at 1–13.

124. *Third*, Phibro submitted written responses to the questions posed by panel members at the public meeting. *See Phibro Animal Health Corporation Responses to Panel Member Questions at the March 10, 2022 Part 15 Hearing (FDA Public Meeting)* (June 9, 2022) (attached as **Exhibit 17**). For example, Phibro confirmed that it was "aware of no reports of cancer in humans or swine associated with carbadox," which is "consistent both with what Phibro's studies definitively established and with carbadox's conditions of use." *Id.* at 1.

125. Documents obtained through the Freedom of Information Act make clear that CVM was not interested in considering Phibro's evidence. In private correspondence, CVM officials agreed Phibro "may be right" about the disputed scientific issues, but nevertheless stressed that "we aren't changing our mind" about the regulatory method. **Exhibit 15** at 13, 23. According to these officials, it was a "big waste of time" to hold the March 2022 public meeting because doing so "just delay[ed] the inevitable." **Exhibit 10** at 7, 14. When one of the officials mentioned an alternative approach, under which CVM would address its concerns by "prolonging the" withdrawal period "to 72 days again," the CVM official who co-chaired the public meeting flippantly replied "lol." **Exhibit 15** at 28–29.

VIII. FDA Issues Final Order Revoking Approved Carbadox Regulatory Method.

126. On November 7, 2023, FDA issued the Revocation Order, a final order that revoked the approved carbadox regulatory method, effective immediately. *See* 88 Fed. Reg. at 76,760. Consistent with the two-step scheme outlined in the 2020 Proposed Order, FDA simultaneously initiated a new proceeding (the "2023 NOOH") "proposing to withdraw approval of all new animal drug applications for use of carbadox based on the lack of an approved method." *Id.* at 76,761; *see Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug*

Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing, 88 Fed. Reg. 76,756 (Nov. 7, 2023).

127. Unlike the 2020 Proposed Order, which was issued by CVM, the Revocation Order was signed by an FDA official (FDA's Deputy Commissioner for Policy, Legislation, and International Affairs). The content of the Revocation Order, however, makes clear that CVM was the de facto decision maker. For example, the Revocation Order explains that the regulatory method is being revoked because of CVM's determinations and conclusions, without any suggestion of a meaningful independent assessment by FDA. *See, e.g.*, 88 Fed. Reg. at 76,763–66. The Revocation Order even refers to "CVM's decision to revoke the method" and states that "CVM is addressing the adequacy of the approved method for carbadox before relying on the Delaney Clause to take action to withdraw the NADAs." *Id.* at 76,767. Accordingly, although the Revocation Order euphemizes CVM's involvement as "appropriately advising on this order," *id.* at 76,768, and describes the decision to revoke the regulatory method as "FDA's," *id.* at 76,767, it is apparent that CVM called the shots. As a result, the disputed scientific and legal issues were decided by the same agency component that was also prosecuting the action to remove carbadox from the market. *See* ¶¶ 11, 98–103, *supra*.

128. Like the 2020 Proposed Order, the Revocation Order does not allege that carbadox is unsafe, either for pigs or humans who consume pork products. That would have contradicted CVM's consistently and publicly issued guidance that there is no need for consumers to alter their dietary choices due to concerns about the carbadox regulatory method. *See Questions and Answers Regarding Carbadox*, *supra* (stating that "the agency is not recommending that people make changes in their food choices during the time that CVM is working to remove the drug from the market").

129. Instead, the Revocation Order turns on the application of narrow, technical provisions of the FDA regulations that implement the DES Proviso. Specifically, in the Revocation Order, CVM asserts that the approved regulatory method must be revoked because "data and information submitted since 1998 . . . do not provide information needed to establish the relationship between QCA [i.e., the marker residue under the approved regulatory method] and the residue of carcinogenic concern." 88 Fed. Reg. at 76,764. CVM thus determines there is no "method for measuring a marker residue with a limit of detection at or below the R_m" in accordance with the applicable regulations. *Id.* at 76,764–65.

130. The Revocation Order also applies the same reasoning to reject the two alternative methods that Phibro proposed: the U.S. Department of Agriculture Food Safety and Inspection Service ("FSIS") method (which uses QCA as a marker residue)[7] and the Canadian Food Inspection Agency method (which uses desoxycarbadox as a marker residue). *See id.* at 76,765–66.

131. The Revocation Order's conclusion that it is impossible to establish an R_m for QCA (or any other marker residue) is based on at least two unsupported premises.

132. *First*, the Order is based on CVM's view that there is insufficient data addressing intermediate metabolites of carbadox—*i.e.*, metabolites of carbadox other than desoxycarbadox and QCA. *Id.* at 76,765. But the Order does not grapple with evidence—including in the Zhang study—that these metabolites are present only fleetingly and rapidly decay. The Zhang study could no longer detect any of these metabolites within 24 hours after dosing, and well-established

[7] *See* https://www.fsis.usda.gov/sites/default/files/media_file/2020-09/CLG-CBX4.pdf.

principles of chemistry demonstrate that these metabolites further deplete to infinitesimally small levels, approaching zero, by three weeks after dosing.

133. *Second*, the Order presumes that carbadox residues bound to tissue proteins are carcinogenic and should be counted toward the residue of carcinogenic concern. *See* 88 Fed. Reg. 76,765–66. But that presumption is contradicted by Phibro's 2016 study demonstrating that *none* of the carbadox residues that are bound to tissue proteins are compounds of carcinogenic concern and is inconsistent with basic principles of chemistry. In particular, the study shows that at the end of the withdrawal period the only bound residue is QCA, which FDA acknowledges is safe.

134. The Revocation Order also attempts to defend the "process" that was used to revoke the carbadox regulatory method. *See id.* at 76,766–68.

135. The Order claims that "[t]he method revocation and withdrawal of NADA approvals are not so intertwined as to require a hearing on revocation under the statute or FDA's regulations." *Id.* at 76,767. Yet at the same time, the Order acknowledges that one proceeding will be bound by the other: The Order resolves as a "threshold matter" the "adequacy of the approved method" *before* "proceeding to an NOOH on withdrawal of the drug's approval." *Id.* at 76,766. And, as explained above, both the FDCA and FDA regulations provide that approval for an animal drug with carcinogenic potential must be withdrawn if there is no longer an FDA-approved regulatory method. *See* ¶ 48, *supra*.

136. The Order also justifies proceeding by declaratory order on the basis that the FDCA requires an evidentiary hearing for an NADA withdrawal rather than on the so-called "interlocutory revocation" of a regulatory method. 88 Fed. Reg. at 76,767. But the Order makes clear that any NADA withdrawal hearing will address only "*new or additional* data to support the approved method or another approvable method." *Id.* at 76,769 (emphasis added). In other words,

the Order dictates that any hearing on the NADA withdrawal will *not* consider the evidence summarily discussed in the Order—including "studies submitted to the 2003 JECFA, the 2008 study, the 2016 [Phibro] studies, [or any] other comments and analyses provided by" Phibro before November 2023. *Id.* at 76,765.

137. The Order asserts that Phibro was provided with "a meaningful opportunity to be heard" because it had the "opportunity to provide comments and other information" and to participate in a "public hearing." *Id.* at 76,767. The Order further maintains that CVM is "appropriately advising on this order" and that CVM's "involvement does not infect any subsequent proceedings with any bias." *Id.* at 76,768.

138. But the Order does not acknowledge that before, during, and after those proceedings, CVM has publicly announced that it is "working to remove [carbadox] from the market"; that CVM officials remarked that it was a "big waste of time" to consider Phibro's evidence because "we aren't changing our mind" and the revocation of the regulatory method is "inevitable"; or that during the public meeting, the CVM officials privately ridiculed Phibro's representative while she presented the company's evidence and legal arguments, again showing that the agency had predetermined the outcome of the proceeding. *See* ¶¶ 104, 116, 125, *supra*.

139. Finally, to justify proceeding without an evidentiary hearing, the Revocation Order cites "two previous occasions when FDA withdrew approval" for animal drugs under the Delaney Clause and DES Proviso. *Id.* at 76,767. But in both of those instances—first, for DES, and second, for nitrofurans—FDA provided the drug sponsor with a formal, evidentiary hearing on the adequacy of the regulatory method *before* withdrawing the drug approval. *See* ¶ 60, *supra*. The Order cites no previous example where a regulatory method was revoked by declaratory order *without* an evidentiary hearing. What is more, with respect to DES, when FDA initially sought to

withdraw its approval of that drug and revoke the relevant regulatory method without holding an evidentiary hearing, the D.C. Circuit set aside the agency's action. *See* ¶¶ 54–56, *supra*.

IX. FDA Denies Phibro's Citizen Petition.

140. On November 2, 2023, FDA denied Phibro's citizen petition. A copy of FDA's Citizen Petition Denial Order is attached as **Exhibit 18**.[8] Although the Citizen Petition Denial Order refers to determinations made by "FDA," the Order was signed by a CVM official.

141. In denying Phibro's citizen petition, FDA rejected Phibro's request that the agency refrain from finalizing, and withdraw, the 2020 Proposed Order on similar grounds to those offered in the Revocation Order. *Id.* at 1. In particular, the Citizen Petition Denial Order rejects Phibro's arguments that under the FDCA, agency precedent, the APA, and the Due Process Clause, FDA is required to afford Phibro a formal evidentiary hearing before an impartial decisionmaker before revoking approval for the carbadox regulatory method. *Id.* at 1.

142. Several aspects of the Citizen Petition Denial Order are particularly relevant here.

143. *First*, the Citizen Petition Denial Order acknowledges that CVM was "involved in" FDA's decisionmaking with respect to the Revocation Order, *id.* at 13—a point further underscored by the Revocation Order's repeated statements that *CVM*, rather than *FDA*, is the agency responsible for the revocation of approval for the carbadox regulatory method. *See* ¶ 127, *supra*.

[8] In a separate response dated November 3, 2023, FDA also denied Phibro's November 2020 stay petition. A copy of FDA's final response to the stay petition (the "Stay Petition Denial Order") is attached as **Exhibit 19**. In denying the stay petition, FDA determined, among other things, that the Revocation Order does not irreparably harm Phibro because it does not prevent Phibro from marketing carbadox during the pendency of the 2023 NOOH proceeding. *Id.* at 2 & n.3. FDA also emphasized, as it did in the Revocation Order, that Phibro would need to present "*new or additional evidence* regarding the adequacy of the [1998 regulatory] method or of another method . . . in its request for hearing in response to the 2023 NOOH." *Id.* at 11–12 (emphasis added).

144. *Second*, the Citizen Petition Denial Order underscores that the Revocation Order precludes Phibro from raising most of its evidence in the 2023 NOOH proceeding. According to FDA, the Revocation Order "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 [desoxycarbadox] methods." Citizen Petition Denial Order at 8–9 (emphasis added). In other words, the vast majority of Phibro's data and evidence undermining FDA's central justification for withdrawing the carbadox NADAs (including Phibro's 2020 submissions) will be off the table and never considered by an impartial adjudicator, contrary to the framework adopted by the FDCA and codified in FDA's Part 12 regulations.

145. *Third,* the Citizen Petition Denial Order concedes that by revoking carbadox's regulatory method, CVM has made a "threshold finding," and that the subsequent withdrawal of carbadox "depends on" that "initial finding." *Id.* at 11; *see also id.* at 12 (touting CVM's "interest in resolving threshold matters at the outset"). The Order characterizes this as a "stepwise approach," *id.* at 13, and claims that it is justified by the need for "administrative efficiency," *id.* at 14.

146. *Fourth*, the Citizen Petition Denial Order—which is signed by CVM's Deputy Center Director—asserts that CVM's "prior involvement" in the carbadox proceedings has not "infect[ed]" the proceedings "with bias." But the Order does not acknowledge the evidence that CVM has prejudged the issues and has displayed hostility to Phibro, carbadox's sponsor. *See* ¶¶ 104, 116, 125, *supra*.

CLAIMS FOR RELIEF

COUNT I: Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)
(Denial of Hearing on Regulatory Method Contrary to FDCA & FDA Regulations)

147. Phibro re-alleges and incorporates by reference each allegation contained in the preceding paragraphs as though fully set forth herein.

148. The APA provides that the Court "shall . . . hold unlawful and set aside agency action" that is "not in accordance with law." 5 U.S.C. § 706(2)(A). The APA further calls for vacatur of agency action taken "without observance of procedure required by law," that is "contrary to constitutional right, power, privilege, or immunity," or that exceeds the agency's "statutory jurisdiction, authority, or limitations." 5 U.S.C. § 706(2)(B)-(D).

149. HHS, FDA, and CVM are "agencies" under the APA, 5 U.S.C. § 551(1), and the Revocation Order constitutes final, reviewable "agency action" for which Phibro "has no other adequate remedy in a court," 5 U.S.C. §§ 551(13), 704.

150. The FDCA provides that FDA "shall issue an order approving" an NADA only "after" FDA provides "notice and opportunity for hearing" and "finds" that various conditions do not apply. 21 U.S.C. § 360b(d)(1). Those prerequisite conditions for approval include the Delaney Clause and DES Proviso, such that FDA must make "find[ings]" based on a "hearing" either that the relevant animal drug is not carcinogenic or that "no residue of such drug will be found" using an approved regulatory method.

151. The FDCA includes a symmetrical set of provisions when it comes to the *withdrawal* of FDA approval for a NADA. The statute provides that FDA "shall . . . issue an order withdrawing approval" of a NADA only "after" FDA provides "notice and opportunity for hearing to the applicant" and "finds" that at least one of the conditions for withdrawal applies. 21 U.S.C. § 360b(e)(1).

152. As relevant here, FDA must withdraw its approval of a NADA if it "finds" "after" "notice and opportunity for hearing" that "new evidence not contained in [the NADA] or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that" the Delaney Clause "applies to such drug" (and that the DES Proviso does not). 21 U.S.C. § 360b(e)(1)(B).

153. Moreover, FDA regulations prescribe specific procedures that CVM must follow before, during, and after a withdrawal "hearing." CVM must provide a formal "Part 12" evidentiary hearing with an impartial adjudicator and the opportunity to cross-examine witnesses. *See* 21 C.F.R. pt. 12.

154. Under the governing statute and implementing regulations, FDA cannot withdraw an NADA approval under the Delaney Clause and DES Proviso until "after" it has made factual "find[ings]" based on a formal, evidentiary "hearing" on the applicability of those provisions. *See, e.g.*, *Hess & Clark*, 495 F.2d at 995 (explaining that the approval and revocation of NADAs and regulatory methods rise and fall together when "withdrawal of [NADA] approval" and "revocation of use regulations" are "inextricably united"); *Chemetron*, 495 F.2d at 1000 (explaining that the "mandate in *Hess* requir[es] the agency to proceed to a hearing on . . . issues" such as factual questions surrounding regulatory methods).

155. The Challenged Orders circumvent this requirement by declaring that there is no valid regulatory method for carbadox—and thus determining the applicability of the Delaney Clause and DES Proviso—*without* providing Phibro with a formal evidentiary hearing on that issue.

156. Now that FDA has revoked approval for the carbadox regulatory method, only two scenarios are possible, both of which are unlawful under the FDCA.

157. The first possibility is that FDA will deny Phibro's request for a hearing in the 2023 NOOH proceeding altogether, claiming that—in light of the Revocation Order—there is no longer any "genuine and substantial issue of fact for resolution at a hearing." 21 C.F.R. § 12.24(b)(1). CVM has suggested from the outset that this is its planned course of action. For example, the agency has stated that rescinding approval for the regulatory method is "the most straightforward and least resource-intensive process for removing carbadox from the market." **Exhibit 2** at 4; *see also* **Exhibit 3** at 3 (December 9, 2019, document admitting that "CVM decided that the most straightforward and expeditious way to remove carbadox from the market is to revoke the approved regulatory method for carbadox").

158. The second possibility is that FDA will grant Phibro's request for a hearing in the 2023 NOOH proceeding, but will (per the Revocation Order) limit that hearing to addressing "*new or additional* data to support the approved method or another approvable method." 88 Fed. Reg. at 76,769 (emphasis added). Under the circumstances—where FDA has already purported to address all of Phibro's evidence as of November 2023 regarding the regulatory method in the Challenged Orders—limiting the scope of a future NOOH hearing to "new or additional data" would mean that the vast majority of the evidence undermining FDA's justification will be off the table and never reviewed by an impartial adjudicator as is required by statute and regulation.

159. Such a hearing would not account for all "evidence not contained in [the carbadox NADAs] or not available to the Secretary until after [the NADAs were] approved, or tests by new methods . . . , evaluated together with the evidence available to the Secretary when the application[s] w[ere] approved," as the statute requires. 21 U.S.C. § 360b(e)(1)(B).

160. Under the plain terms of the Challenged Orders, no other outcome is possible. For example, the Revocation Order does not leave open the possibility that FDA will grant Phibro the formal evidentiary hearing on the carbadox regulatory method that Phibro is entitled to by statute and regulation.

161. Because the Challenged Orders circumvent the requirements of the FDCA statute and implementing regulations, this Court should hold that the Orders are unlawful and set them aside. *See* 5 U.S.C. § 706(2)(A).

COUNT II: Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)
(Lack of Impartial Adjudicator)

162. Phibro re-alleges and incorporates by reference each allegation contained in the preceding paragraphs as though fully set forth herein.

163. The APA provides that the Court "shall . . . hold unlawful and set aside agency action" that is "not in accordance with law." 5 U.S.C. § 706(2)(A). The APA further calls for vacatur of agency action taken "without observance of procedure required by law," that is "contrary to constitutional right, power, privilege, or immunity," or that exceeds the agency's "statutory jurisdiction, authority, or limitations." 5 U.S.C. § 706(2)(B)-(D).

164. As described in Count I, the FDCA and FDA's implementing regulations provide that FDA cannot withdraw a NADA approval under the Delaney Clause and DES Proviso until "after" it has made factual "find[ings]" based on a formal evidentiary "hearing." 21 U.S.C. § 360b(e)(1); 21 C.F.R. pt. 12; 21 C.F.R. § 514.201. The objective of the formal evidentiary hearing is "the fair determination of relevant facts." 21 C.F.R. § 12.87(a). FDA's regulations also require that the formal evidentiary hearing be held before an impartial adjudicator, *id.* §§ 12.60, 12.70, 12.75, 12.87, with a strict separation between investigative and adjudicative personnel, *id.* §§ 10.55(b)(2) & (c), 12.60. After the hearing, the impartial adjudicator must prepare and file an

initial decision, which becomes the final decision of the FDA Commissioner by operation of law unless a participant files exceptions or the Commissioner files a notice of review. *Id.* § 12.120(e).

165. Moreover, under the APA and due process, parties whose rights are affected by an agency adjudication are "entitled to a hearing before a neutral decision-maker," *James Madison Ltd. ex rel. Hecht v. Ludwig*, 82 F.3d 1085, 1099 (D.C. Cir. 1996), and an administrative hearing must give parties an "impartial tribunal" and "fair and equal opportunity to present exhibits and witnesses designed to establish the legitimacy of their argument," *Cinderella Career & Finishing Schs., Inc. v. FTC*, 425 F.2d 583, 587, 592 (D.C. Cir. 1970); *see also, e.g.*, *Finer Foods, Inc. v. USDA*, 274 F.3d 1137, 1140 (7th Cir. 2001) ("The Fruit and Vegetables Program Branch appears to be a principal in the dispute, not a neutral arbiter; and although this is not a formal hearing on the record subject to § 4 of the Administrative Procedure Act, 5 U.S.C. § 554, it is certainly an informal adjudication in which the decision should have been made after a hearing by someone without a stake in the outcome.").

166. In addition to failing to provide the required evidentiary hearing, Defendants also deprived Phibro of its right to have the regulatory-method issue adjudicated by an impartial decisionmaker, as required by the governing statute and regulations, the APA, and due process. If FDA had not impermissibly bifurcated the proceeding to rescind the approved regulatory method from the proceeding to withdraw approval of the carbadox NADAs, the disputed factual issues relating to the adequacy of the regulatory method would have been decided by an impartial adjudicator, with a strict separation of functions between investigative and adjudicative personnel. *See* 21 U.S.C. § 360b(e); 21 C.F.R. §§ 10.55(b)(2) & (c), 12.60. This arrangement would have ensured that CVM—the FDA component organization seeking to withdraw the NADA

approvals—would not be the decisionmaker regarding disputed scientific and legal issues raised at the hearing, or have undue access to and influence over the decision maker.

167. CVM proposed the Revocation Order, and, as the 2020 Proposed Order and the broader history described above shows, CVM predetermined the outcome of that proceeding even before it began. In December 2019, shortly before CVM initiated the proceedings to revoke approval for the carbadox regulatory method, agency officials stated that "CVM [has] decided that the most straightforward and expeditious way to remove carbadox from the market is to revoke the approved regulatory method for carbadox." **Exhibit 3** at 3. CVM doubled down on that position in the 2020 Proposed Order, stating that upon finalizing the order, the agency "intend[ed] to publish in the Federal Register [a NOOH] proposing to withdraw approval of all new animal drug applications for use of carbadox based on the lack of an approved [regulatory] method." 85 Fed. Reg. at 43,854. As a CVM spokesperson later explained to *Bloomberg News*, this approach reflected a view that "going after the testing method . . . is the most straightforward and least resource-intensive process for removing carbadox from the market." **Exhibit 2** at 4. FDA openly acknowledged this agenda in a notice posted on the agency's website, declaring before, during, and after the proceedings below that "CVM is working to remove the drug from the market." *See* ¶ 104, *supra*.

168. The March 2022 public meeting regarding the carbadox regulatory method suffered from the same procedural defects. As explained above, there was no separation between CVM's presenter and the panelists conducting the hearing. For example, CVM's presenter, Dr. Julia Oriani, solicited and obtained feedback on her presentation from a panelist, Dr. Jonathan Greene, **Exhibit 11** at 1; **Exhibit 14** at 1, before the hearing occurred and suggested question topics to Greene, even as both individuals recognized that they "shouldn[']t discuss" these issues with each

other, **Exhibit 9** at 4. Others at CVM complained to Greene that the hearing was a "big waste of time" and was "just delaying the inevitable," **Exhibit 10** at 7, 14, because "we aren't changing our mind," even if Phibro "may be right" about the disputed issues, **Exhibit 15** at 13, 23. In response, Greene expressed agreement. **Exhibit 10** at 15. Rather than considering Phibro's evidence, CVM officials sent each other Internet memes during the meeting and bragged to one another about concealing new study evidence from Phibro. **Exhibit 15** at 31–34 (discussing a meme sent between officials during the meeting); **Exhibit 13** at 19–30, 33–34 (bragging about concealing new study evidence from Phibro).

169. Although the Revocation Order suggests that the decision to revoke the regulatory method was FDA's and that CVM merely "advis[ed] on th[e] order," 88 Fed. Reg. at 76,768, the Revocation Order elsewhere refers to "CVM's decision to revoke the method," *id.* at 76,767. Even if the revocation decision is attributable to FDA, the records described above show that there was no separation of functions whatsoever between adjudicatory and investigative personnel and no impartial decision maker. Moreover, "a disinterested observer" could readily "conclude that the agency has in some measure adjudged the facts as well as the law . . . in advance of hearing [the matter before it]." *Cinderella Career & Finishing Sch., Inc.*, 425 F.2d at 591 (alteration added).

170. Where "an initial determination is made by a party acting in an enforcement capacity, due process may be satisfied by providing for a neutral adjudicator to conduct a *de novo* review of all factual and legal issues." *Concrete Pipe & Prods. Of Cal., Inc. v. Construction Laborers Pension Trust for. S. Cal.*, 508 U.S. 602, 618 (1993) (quotation marks omitted). Here, no such *de novo* review by a neutral adjudicator was provided or will be provided in connection with the proceeding to withdraw the carbadox NADAs because the Challenged Orders take off the

table Phibro's evidence as of November 2023 regarding the regulatory method. *See* ¶¶ 138, 158–60, *supra*.

171. Defendants' failure to provide an impartial decision maker for the method-revocation proceeding violated Phibro's rights under the APA, FDCA, and FDA's implementing regulations, and due process.

172. Because the Challenged Orders were issued without observance of procedures required by law, exceeded Defendants' statutory authority, and constituted agency action taken not in accordance with law, the Court should set them aside and remand for further proceedings. *See* 5 U.S.C. § 706(2).

COUNT III: Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)(A)
(Arbitrary and Capricious Departure from Past FDA Practice)

173. Phibro re-alleges and incorporates by reference each allegation contained in the preceding paragraphs as though fully set forth herein.

174. The APA provides that a court "shall . . . hold unlawful and set aside agency action" that is "arbitrary, capricious, an abuse of discretion or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

175. Among other things, the APA imposes a "basic procedural requiremen[t] . . . that an agency must give adequate reasons for its decisions." *Encino Motorcars, LLC v. Navarro*, 579 U.S. 211, 221 (2016). "Reasoned decision making . . . necessarily requires the agency to acknowledge and provide an adequate explanation for its departure from established precedent." *Dillmon v. Nat'l Transp. Safety Bd.*, 588 F.3d 1085, 1089–90 (D.C. Cir. 2009).

176. So far as Phibro is aware, FDA has *never* followed the two-step approach adopted by the Challenged Orders here—i.e., first revoking an approved drug's regulatory method without

holding an evidentiary hearing, and then proposing to withdraw marketing authorization for the drug based solely on the absence of an approved regulatory method.

177. Indeed, the Challenged Orders' novel approach departs from past agency practice. As described above, *see* ¶¶ 54–60, *supra*, although FDA initially failed to afford the DES sponsors the hearing they was due, the D.C. Circuit ruled against FDA, *see Hess & Clark*, 495 F.2d at 995; *Chemetron Corp.*, 495 F.2d at 1000, and FDA remedied its error by providing the sponsors with a formal evidentiary hearing. In vacating FDA's initial withdrawal orders, the court expressly rejected FDA's attempts to bifurcate consideration of the regulatory method and NADA withdrawals, explaining that the method revocation was "inextricably united to . . . withdrawal of approval," such that the FDCA "*require*[*s*] the Commissioner to revoke [regulatory methods] *when* he revokes approval of an NADA." *Hess & Clark*, 495 F.2d at 995 (emphasis added). The court further explained that where new evidence suggested that the approved method is insufficient to detect the residue marker, a hearing is the appropriate process. *See Chemetron Corp.*, 495 F.2d at 999 (new evidence from a method "detect[ing] residues" is a "basic matte[r] . . . requiring a hearing"). The DES sponsors were ultimately provided a formal evidentiary hearing—without limitation on the evidence they could present—in accordance with 21 U.S.C. § 360b(e)(1) and FDA's Part 12 regulations.

178. Likewise, when FDA withdrew approvals for a class of chemicals known as "nitrofurans," FDA issued a NOOH and then provided the nitrofurans sponsors a formal evidentiary hearing that addressed whether the Delaney Clause applied (nitrofurans previously had not been considered carcinogenic) and whether an adequate regulatory method triggered the DES Proviso. *See* 56 Fed. Reg. at 41,904–11. As with the DES precedent, FDA followed the proper statutory process in withdrawing the nitrofurans approvals by holding an evidentiary hearing to

consider the applicability of the Delaney Clause and DES Proviso—including the existence of any valid, regulatory method. *See* 21 U.S.C. § 360b(e)(1)(B), (d)(1)(I).

179. FDA's two-step scheme to revoke the carbadox method and then separately withdraw NADA approvals on that basis departs from these precedents. FDA did not afford Phibro a formal evidentiary hearing regarding the validity of the carbadox regulatory method, and likewise has gone to great lengths to consider the regulatory method and the NADA approvals in separate proceedings. FDA adopted this two-step scheme after Phibro submitted new data and evidence reconfirming the safety of carbadox in 2016. Following Phibro's submission, the agency rescinded the 2016 NOOH (without conducting a hearing) and shifted to a new procedural strategy to remove the carbadox from the market in the least resource-intensive way. *See* ¶¶ 90–97, *supra*.

180. The Challenged Orders erroneously assert that their bifurcated approach is consistent with past agency practice. Contrary to FDA's assertion, *Hess & Clark* and *Chemetron* do not counsel in favor of revoking a method before withdrawing a NADA approval—they foreclose FDA's two-step approach and strengthen Phibro's argument that it was entitled to an evidentiary hearing on the carbadox regulatory method. *See* ¶ 56, *supra*. That immediately following *Hess & Clark* and *Chemetron* FDA itself acknowledged that a hearing on NADA withdrawal "could include" consideration of the regulatory method confirms this point and belies FDA's current argument. *See* ¶ 58, *supra*. Nor is it relevant that the DES withdrawal and nitrofurans withdrawals involved both the Delaney and general safety clauses, *see* ¶ 139, *supra*, as either withdrawal justification triggers the same process requirements that Phibro alleges were violated here, *see* 21 U.S.C. § 360b(e)(1)(B).

181. Finally, FDA wrongly brushed aside the DES precedent because it preceded the regulations that implement the Delaney Clause and DES Proviso. *See* ¶ 139, *supra*. Those

regulations further define the *substantive* standards that govern the application of those provisions, but they did not change the preexisting and statutorily guaranteed *process* a drug sponsor is due when application of those provisions is in question. By statute, Phibro is entitled to a formal evidentiary hearing to address the applicability of the Delaney Clause and DES Proviso as part of the NADA withdrawal process, *see supra* Count I, and the implementing regulations did not—and could not—alter that basic procedural requirement.

182. Absent acknowledgement of the change and a supportable justification for the departure from agency precedent, *see Dillmon*, 588 F.3d at 1089–90, Defendants have not articulated a reasoned explanation for the Challenged Orders, including a rational connection between the facts found and the choice made.

183. Defendants have acted arbitrarily and capriciously in violation of the APA, *see* 5 U.S.C. § 706(2)(A), such that this Court should hold the Challenged Orders unlawful and set them aside.

COUNT IV: Violation of Administrative Procedure Act, 5 U.S.C. § 706(2)(A)
(Arbitrary and Capricious Agency Action—Contrary to the Record)

184. Phibro re-alleges and incorporates by reference each allegation contained in the preceding paragraphs as though fully set forth herein.

185. The APA provides that a court "shall . . . hold unlawful and set aside agency action" that is "arbitrary, capricious, an abuse of discretion or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

186. Among other things, the APA requires that the agency "examine the relevant data and articulate a satisfactory explanation for its action." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). An agency's decision is arbitrary and capricious if, among other things, the agency "offered an explanation for its decision that runs counter to the

evidence before the agency," *id.*, or changed its position without "show[ing] that there are good reasons for the new policy." *Encino Motorcars, LLC*, 579 U.S. at 221 (quoting *FCC v. Fox Televisions Stations, Inc.*, 556 U.S. 502, 515 (2009)).

187. The Challenged Orders are also arbitrary and capricious because they are inconsistent with the record evidence. Contrary to Defendants' conclusion that there is no data to establish a relationship between QCA and the residue of potential carcinogenic concern and that QCA therefore is not an appropriate marker residue, a substantial body of evidence shows a clear relationship between the presence of carbadox and desoxycarbadox (the only residue compound that persists in a meaningful way) on the one hand, and QCA on the other.

188. Phibro has established, through cutting-edge scientific methods and substantial investments made at CVM's request, that no unsafe residue of carbadox is detectable in swine tissue at the conclusion of the FDA-prescribed withdrawal period.

189. Data submitted by Phibro demonstrates that QCA is an appropriate marker residue, and that measuring QCA accurately identifies the levels of carbadox and desoxycarbadox present in swine tissue. In light of this data, the QCA testing method approved in 1998 remains a reliable means of ensuring that carbadox residues reach safe (S_m) levels before the applicable withdrawal dates, and that no carbadox residues will be found at the time of slaughter (i.e., at the conclusion of the FDA-mandated withdrawal periods).

190. Defendants' conclusion that there is no data to establish a relationship between QCA and the residue of potential carcinogenic concern is contrary to the record. The Challenged Orders maintain that desoxycarbadox "is only one metabolite of carbadox and therefore just one component of the residue of carcinogenic concern," and that an R_m for the marker residue used to detect the presence of potential carcinogens could not be set unless it "accounted for the residue

of carcinogenic concern." 88 Fed. Reg. at 76,765. But the record demonstrates that the other residue compounds cited by FDA decay much more quickly than either desoxycarbadox or QCA, such that—at relevant times postdosing—they would not contribute to the residue level.

191. Specifically, the Zhang study regarding the metabolism and residue depletion of carbadox showed that any other detectable residue compounds decayed rapidly to below the study's limit of detection within 24 hours after dosing, at an apparent rate of decay substantially faster than desoxycarbadox or QCA. The Revocation Order stated that the Zhang study did not provide the data necessary to establish an R_m value for QCA because the method used in that study was not capable of detecting carbadox metabolites below 20 parts per billion, a concentration that is greater than the safe (S_m) level. *Id.* at 76,766. That conclusion ignores reality: Extrapolating from the rate of decay evidenced by the Zhang study's data using well-accepted principles of chemistry, it is clear that the residue compounds continue to decay after falling below the study's limit of detection and reach infinitesimally small levels—on the order of or lower than *10 trillionths* (1×10^{-11}) of a *part per billion*—by three weeks postdosing, before the time at which desoxycarbadox reaches the safe (S_m) level of 0.915 parts per billion. In other words, at relevant times postdosing, these other compounds would not contribute to the residue level. The Revocation Order unreasonably ignored this evidence. *See Genuine Parts Co. v. EPA*, 890 F.3d 304, 313 (D.C. Cir. 2018) (it is arbitrary and capricious for an agency "to rely on portions of studies in the record that support its position, while ignoring [portions of] those studies that do not").

192. Despite ample evidence before it to establish an R_m value for QCA, FDA refused to set this value, due to its insistence—contrary to the record—that it could not account for the short-lived intermediate metabolite compounds. Defendants have therefore not articulated a

satisfactory explanation, including a rational connection between the facts found and the choice made. *See* 5 U.S.C. § 706(2)(A); *State Farm*, 463 U.S. at 43.

193. The Challenged Orders also unreasonably reject the 1998 regulatory method for another reason: In deciding to revoke approval for that method on the ground that FDA has not set an R_m value, FDA presumed that carbadox residues bound to tissue proteins are carcinogenic and should be counted toward the residue of carcinogenic concern. 88 Fed. Reg. at 76,765–66. That presumption is false, as shown by Phibro's 2016 study demonstrating that *none* of the carbadox residues that are bound to tissue proteins are compounds of carcinogenic concern. It also defies basic principles of chemistry, as Phibro explained in its June 2022 submission. *See Phibro Reply to the January 6, 2022 CVM Response to Phibro Animal Health Corporation's September 18, 2020 Comments on CVM's July 20, 2020 Proposed Order to Revoke the Regulatory Method for Carbadox* (June 9, 2022), at 66, *available at* https://www.regulations.gov/comment/FDA-2021-N-1326-2214 (attached as **Exhibit 20**). Defendants' conclusions to the contrary not only inexplicably depart from its prior stance that bound residues are *not* carcinogenic, but also run counter to the evidence (and basic science) before it.

194. In short, Defendants have acted arbitrarily and capriciously by withdrawing carbadox's regulatory method rather than relying on the available data to identify the R_m for QCA. *See* 5 U.S.C. § 706(2)(A).

195. The Challenged Orders' assessment of the alternative regulatory methods proposed by Phibro is likewise arbitrary and capricious.

196. In prior proceedings, FDA has considered and adopted a regulatory method for potential carcinogens where, as here, a suitable analytical method is available. *See, e.g.*, *Animal Drugs, Feeds, and Related Products; Eprinomectin; N-Methyl-2-Pyrrolidone*, Final Rule, 76 Fed.

Reg. 72,617 (Nov. 25, 2011); 21 C.F.R. § 500.1410; *Food Substances Affirmed as Generally Recognized as Safe in Feed and Drinking Water of Animals: 25-Hydroxyvitamin D3*, Final Rule, 72 Fed. Reg. 12,560, 12,562–63 (Mar. 16, 2007); *Tobacco Product Standard for N-Nitrosonornicotine Level in Finished Smokeless Tobacco Products*, Proposed Rule, 82 Fed. Reg. 8,004–05 (Jan. 23, 2017). Indeed, the DES Proviso assumes that FDA will prescribe or approve a regulatory method if any viable method is available, *see* 21 U.S.C. § 360b(d)(1)(I), a point the D.C. Circuit has similarly suggested in connection with a related provision in § 360b(i), *see Hess*, 945 F.2d at 995. FDA embraced that position in the DES proceeding, concluding that the agency "must approve an analytical method if an appropriate one is presented." 44 Fed. Reg. at 54,860.

197. Despite FDA's usual practice, the Revocation Order rescinds the approved carbadox regulatory method without replacing that method with one of the alternative regulatory methods Phibro proposed (e.g., the U.S. Department of Agriculture method based on a QCA marker, or the Canadian Food Inspection Agency method based on a desoxycarbadox marker; both currently in use).

198. The Challenged Orders rejected Phibro's proposed viable alternatives because, in CVM's view, there is not sufficient data to set an R_m for either QCA or desoxycarbadox due to uncertainty about other carbadox metabolites. *See* ¶¶ 131–32, *supra*. As shown above, however, FDA had sufficient data to set an R_m for either of those substances given the evidence showing that all other carbadox metabolites are short-lived and do not affect the total residue by the relevant withdrawal period. *See* ¶¶ 188–92, *supra*.

199. The Challenged Orders' rejection the viability of the Canadian method is especially unreasonable given CVM's own statement—in a memorandum to the docket in the Revocation Order proceeding—that the Canadian method "has been used successfully for many years."

Exhibit 7 at 8. Having acknowledged the validity of the Canadian method, FDA needed to at least engage with that method rather than merely brushing it aside without meaningful analysis. *See Chamber of Commerce of U.S. v. SEC*, 412 F.3d 133, 144–45 (D.C. Cir. 2005).

200. Because FDA's justifications for dismissing Phibro's proposed alternative methods were erroneous, Defendants failed "to give a reasoned explanation" for their action, *Am. Radio Relay League, Inc. v. FCC*, 524 F.3d 227, 242 (D.C. Cir. 2008) (citation omitted), rendering the Challenged Orders arbitrary and capricious. *See* 5 U.S.C. § 706(2).

201. FDA has repeatedly pivoted, changing direction and unlawfully cutting corners in its push to remove carbadox from the market regardless of the science or evidence.

REQUESTED RELIEF

WHEREFORE, Phibro respectfully requests that this Court:

A. Issue a declaration that the Challenged Orders are arbitrary, capricious, and contrary to law on the grounds recited above;

B. Vacate the Challenged Orders on the grounds recited above;

C. Remand this matter to FDA for further proceedings consistent with the Court's decision; and

D. Award such other relief as this Court deems just and proper.

Respectfully submitted,

/s Kevin F. King

Michael X. Imbroscio (D.C. Bar No. 445474)
Jeannie M. Perron (D.C. Bar No. 456099)
Kevin F. King (D.C. Bar No. 1012403)
Counsel of Record
COVINGTON & BURLING LLP
One CityCenter
850 Tenth Street, NW
Washington, DC 20001-4956
(202) 662-6000
mimbroscio@cov.com
jperron@cov.com
kking@cov.com

January 5, 2024