1. Medicare

Based on CMS data, we estimate that in CY 2024 approximately—
- 14,232 newly enrolling institutional providers will be subject to and pay an application fee; and
- 36,142 revalidating institutional providers will be subject to and pay an application fee.

Using a figure of 50,374 (14,232 newly enrolling + 36,142 revalidating) institutional providers, we estimate an increase in the cost of the Medicare application fee requirement in CY 2024 of $1,057,854 (or 50,374 x $21 (or $709 minus $688)) from our CY 2023 projections.

2. Medicaid and CHIP

Based on CMS and state statistics, we estimate that approximately 30,000 (9,000 newly enrolling + 21,000 revalidating) Medicaid and CHIP institutional providers will be subject to an application fee in CY 2024. Using this figure, we project an increase in the cost of the Medicaid and CHIP application fee requirement in CY 2024 of $630,000 (or 30,000 x $21 (or $709 minus $688)) from our CY 2023 projections.

3. Total

Based on the foregoing, we estimate the total increase in the cost of the application fee requirement for Medicare, Medicaid, and CHIP providers and suppliers in CY 2024 to be $1,687,854 ($1,057,854 + $630,000) from our CY 2023 projections.

We do not anticipate any negative impact on equity from the increase in the application fee amount, which we calculated in accordance with the requirements specified in statute and regulation. Prior application fee increases have had no such discernable effect, and we reiterate that the fee requirement does not apply to individual physicians and non-physician practitioners completing the CMS–855I, who represent the overwhelming preponderance of the more than 2 million Medicare-enrolled providers and suppliers.

The RFA requires agencies to analyze options for regulatory relief of small businesses. For purposes of the RFA, small entities include small businesses, nonprofit organizations, and small governmental jurisdictions. Most hospitals and most other providers and suppliers are small entities, either by nonprofit status or by having revenues of less than $9 million to $47 million in any 1 year. Individuals and states are not included in the definition of a small entity. As we stated in the RIA for the February 2, 2011 final rule (76 FR 5952), we do not believe that the application fee will have a significant impact on small entities.

In addition, section 1102(b) of the Act requires us to prepare a regulatory impact analysis if a rule may have a significant impact on the operations of a substantial number of small rural hospitals. This analysis must conform to the provisions of section 604 of the RFA. For purposes of section 1102(b) of the Act, we define a small rural hospital as a hospital that is located outside of a Metropolitan Statistical Area for Medicare payment regulations and has fewer than 100 beds. We are not preparing an analysis for section 1102(b) of the Act because we have determined, and the Secretary certifies, that this notice would not have a significant impact on the operations of a substantial number of small rural hospitals.

Section 202 of the Unfunded Mandates Reform Act of 1995 (UMRA) also requires that agencies assess anticipated costs and benefits before issuing any rule whose mandates require spending in any 1 year of $100 million in 1995 dollars, updated annually for inflation. In 2023, that threshold was approximately $198 million. The Agency has determined that there will be minimal impact from the costs of this notice, as the threshold is not met under the UMRA.

Executive Order 13132 establishes certain requirements that an agency must meet when it promulgates a proposed rule (and subsequent final rule) that imposes substantial direct costs, benefits, or other effects on state or local governments, or preempts state law, or otherwise has federalism implications. Since this notice does not impose substantial direct costs on state or local governments, the requirements of Executive Order 13132 are not applicable.

In accordance with the provisions of Executive Order 12866, this notice was reviewed by the Office of Management and Budget.

The Administrator of the Centers for Medicare & Medicaid Services (CMS), Chiquita Brooks-LaSure, having reviewed and approved this document, authorizes Chyana Woodyard, who is the Federal Register Liaison, to electronically sign this document for purposes of publication in the Federal Register.

Chyana Woodyard,
Federal Register Liaison, Centers for Medicare & Medicaid Services.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2023–N–4742]

Phibro Animal Health Corp.; Proposal To Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or the Agency), Center for Veterinary Medicine (CVM), is proposing to withdraw approval of all new animal drug applications (NADAs) providing for use of carbadox in medicated swine feed, for which Phibro Animal Health Corp., Glenpointe Centre East, Third Floor, 300 Frank W. Burr Blvd., Suite 21, Teaneck, NJ 07666–6712, is the sponsor, and is announcing an opportunity for the holder of the NADAs to request a hearing on this proposal. This action is based on CVM’s determination that there is no approved regulatory method to detect the residue of carcinogenic concern in the edible tissues of the treated swine.

DATES: The sponsor of the NADAs may submit a written request for a hearing by December 7, 2023. Submit all data, information, and analyses upon which a request for a hearing relies by December 7, 2023. Either electronic or written comments on the notice must be submitted by December 7, 2023.

ADDRESSES: The request for a hearing may be submitted by the sponsor of the NADAs by either of the following methods:

Electronic Submissions
Submit electronic comments in the following way:
- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments to submit your request for hearing. Your request for a hearing submitted electronically, including any attachments to the request for hearing, to https://www.regulations.gov will be posted to the docket unchanged.

Written/Paper Submissions
Submit written/paper submissions as follows:
- Mail/Hand Delivery/Courier (for written/paper request for a hearing): Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
Electronic Submissions

Submit electronic comments in the following way:
• Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be publicly posted, such as confidential business information (e.g., a manufacturing process). The request for a hearing must include the Docket No. FDA–2023–N–4742 for “Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing.” The request for a hearing will be placed in the docket and publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

The sponsor of the NADAs may submit all data and analyses upon which the request for a hearing relies in the same manner as the request for a hearing except as follows:
• Confidential Submissions—To submit any data and analyses with confidential information that you do not wish to be made publicly available, submit your data and analyses only as a written/paper submission. You should submit two copies total of all data and analyses. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of any decisions on this matter. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov or available at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Dockets Management Staff. Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law.

Comments Submitted by Other Interested Parties: For all comments submitted by other interested parties, submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of December 7, 2023. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

• Mail/Hand Delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
• For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA–2023–N–4742 for “Phibro Animal Health Corp.; Proposal to Withdraw Approval of New Animal Drug Applications for Carbadox in Medicated Swine Feed; Opportunity for a Hearing.” Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

FOR FURTHER INFORMATION CONTACT:
Diane Heinz, Center for Veterinary Medicine (HFV–6), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240–402–5692.

SUPPLEMENTARY INFORMATION:

I. Approved NADAs for Use of Carbadox in Swine Feed

Carbadox, a quinoxaline derivative, is a synthetic organic acid antimicrobial. Currently, there are three approved NADAs for use of carbadox in medicated swine feed, either by itself or in combination with other approved new animal drugs. Phibro Animal Health Corp., Glenpointe Centre East, Third Floor, 300 Frank W. Burr Blvd., Suite 21, Teaneck, NJ 07666–6712, is currently the sponsor of all three approved NADAs.

Carbadox is marketed as a Type A medicated article used to manufacture complete Type C medicated feeds that are administered ad libitum (available at all times) to swine. Carbadox is
Ascaris suum

establishment of large roundworm

Salmonella choleraesuis

necrotic enteritis caused by

bacterial swine enteritis (salmonellosis)

hemorrhagic dysentery); for control of

dysentery, bloody scours, or

dysentery, bloody scours, or

carboxylic acid (QCA), the marker residue, in liver of swine (21 CFR 556.100). The

combination products containing carboxadox (carbadox and pyrantel, and carboxadox and oxytetracycline) are also approved for additional indications related to the non-carboxadox active ingredient.

The following three NADAs are approved for the use of carboxadox:

NADA 041–061, originally approved in 1972 (37 FR 20683, October 3, 1972), provides for the use of MECADOX 10 (carbadox) Type A medicated article to manufacture single-ingredient Type C medicated swine feeds for the following conditions of use:

Carboxadox at 10 to 25 grams per ton (g/ton) of feed for increased rate of weight gain and improved feed efficiency; and

Carboxadox at 50 g/ton of feed for control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery); for control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by Salmonella choleraesuis); and for increased rate of weight gain and improved feed efficiency.

In January 1998, CVM approved a supplemental application to NADA 041–061, which included the approved method.

In October 1998, CVM approved an additional supplemental NADA for NADA 041–061, changing the withdrawal period for carboxadox medicated feeds from 70 days to 42 days.

Currently, the withdrawal period for these uses of carboxadox is 42 days (§ 558.115(d)(1)(ii) and (d)(2)(iii) (21 CFR 558.115(d)(1)(ii) and (d)(2)(iii)).

NADA 092–955, originally approved in 1975 (40 FR 45164, October 1, 1975), provides for the use of MECADOX 10 (carbadox) Type A medicated article with BANMINTH (pyrantel tartrate) Type A medicated article to manufacture two-way, combination drug Type C medicated swine feeds for the following conditions of use:

Carboxadox at 10 to 25 g/ton of feed plus oxytetracycline at levels in feed to deliver 10 mg oxytetracycline per pound of body weight for treatment of bacterial enteritis caused by Escherichia coli and S. choleraesuis susceptible to oxytetracycline; for treatment of bacterial pneumonia caused by Pasteurella multocida susceptible to oxytetracycline; and for increased rate of weight gain and improved feed efficiency.

The withdrawal period for the use of this animal drug combination is 42 days (§ 558.115(d)(4); § 558.450(e)(3)(iii)).

II. Basis for Withdrawal of Approval

FDA is providing notice of an opportunity for a hearing (NOOH) on CVM’s proposal to withdraw approval of the NADAs providing for use of carboxadox in medicated swine feeds. New evidence demonstrates that the Delaney Clause in section 512(d)(1)(I) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360b(d)(1)(I)), which requires that no residue of a carcinogenic drug can be found in any edible portion of the animal after slaughter, applies because the Diethylstilbestrol (DES) Proviso exception is no longer met (see section III).

Section 512(e)(1)(B) of the FD&C Act provides grounds for withdrawal of approval of an NADA if new evidence not contained in such application or not available until after such application was approved, tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available when the application was approved, shows that the Delaney Clause, section 512(d)(1)(I) of the FD&C Act, applies to the drug. Under the Delaney Clause, the Secretary shall not approve a new animal drug application if “such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal” (section 512 (d)(1)(I) of the FD&C Act). An exception to this general rule, referred to as the “DES Proviso,” allows for the approval of a carcinogenic new animal drug where FDA finds that, under the approved conditions of use: (1) The drug will not adversely affect the animals treated with the drug, and (2) no residues of the drug will be found by an approved regulatory method in any edible tissues of or in any foods yielded by the animal (section 512(d)(1)(I)(i) through (ii) of the FD&C Act).

Evidence available at the time of the approvals showed that carboxadox was carcinogenic. At the time of the January 1998 supplemental approval, CVM concluded that carcinogenic residues, including desoxycarbadox (DCBX), a known carcinogenic metabolite of carboxadox, depleted quickly (within 72 hours) while QCA residues depleted more slowly (Ref. 1). However, new evidence not available at the time of the approval, including studies conducted by the sponsor and submitted to FDA from 2005 to 2016 and a study conducted by a third party and summarized in a publication in 2022,1 demonstrates that the residue of carcinogenic concern persists longer than previously known (Refs. 2 to 4). Because there is no established relationship between concentrations of QCA measured by the approved method and concentrations of the residue of carcinogenic concern, the approved regulatory method cannot be used to measure the residue of carcinogenic concern.

Elsewhere in today’s Federal Register, FDA is publishing a final order (Ref. 5) revoking the approved regulatory method for carboxadox that measures QCA as a marker residue to detect the presence of any residue of carcinogenic concern (Ref. 6). Currently, therefore, there is no approved regulatory method for carboxadox, and the second prong of the DES Proviso is not met.

III. Background Information Regarding the Regulation of Carcinogenic New Animal Drugs

Under the Delaney Clause of the FD&C Act, the Secretary shall not approve a carcinogenic new animal drug application unless the DES Proviso applies (section 512(d)(1)(I)(i) through (ii) of the FD&C Act). FDA has issued implementing regulations that set the requirements for demonstrating that no residues of the drug will be found by an approved regulatory method in any

Based on residue depletion data submitted by a sponsor, FDA selects a target tissue (the edible tissue selected to monitor for residues in the target animals) and a marker residue (a residue whose concentration is in a known relationship to the concentration of the residues of carcinogenic concern in the last tissue to deplete to the S_{m}) and designates the concentration of the marker residue that the regulatory method must be capable of detecting in the target tissue (§ 500.86(a) through (c)). This value, termed the R_{m}, is the concentration of a marker residue in the target tissue when the residue of carcinogenic concern is equal to S_{m} (§ 500.82(b)). When the marker residue is at or below the R_{m}, the residue of carcinogenic concern in the human diet does not exceed S_{m} (§ 500.86(c)).

A sponsor must submit a regulatory method that is able to detect the marker residue at or below the R_{m} (21 CFR 500.88(b) and 500.84(c)(2)) (“The LOD [Limit of Detection for the regulatory method] must be less than or equal to R_{m}”). If a method is not developed that can detect the marker residue at or below the R_{m}, the requirements of the SOM regulations are not satisfied, and FDA cannot approve the drug. The DES Proviso and FDA’s implementing regulations are satisfied where no marker residue is detectable using the approved regulatory method under the proposed conditions of use of the drug, including the proposed preslaughter withdrawal period (§ 500.84(c)(3)).

**IV. Notice of Opportunity for a Hearing**

CVM is proposing to withdraw approval of the three NADAs that provide for use of carbadox in swine feed because new evidence demonstrates that the drug does not meet the DES Proviso exception to the Delaney Clause. There is currently no approved regulatory method for carbadox.

Therefore, notice is given to Phibro Animal Health Corp., Glenpointe Centre East, Third Floor, 300 Frank W. Burr Blvd., Suite 21, Teaneck, NJ 07666–6712, and to all other interested persons, that the Deputy Commissioner for Policy, Legislation, and International Affairs, Office of Policy, Legislation, and International Affairs proposes to issue an order under section 512(e) of the FD&C Act withdrawing approval of all NADAs providing for use of carbadox in medicated swine feed.

In accordance with section 512 of the FD&C Act and 21 CFR part 514 and under the authority delegated to the Deputy Commissioner for Policy, Legislation, and International Affairs, Office of Policy, Legislation, and International Affairs by the Commissioner of Food and Drugs, Phibro Animal Health Corp., the sponsor, is hereby given an opportunity for a hearing to show why approvals of NADA 941–061, 092–955, and 141–211 should not be withdrawn.

If the sponsor, Phibro Animal Health Corp., wishes to request a hearing, the sponsor must file the following: (1) a written notice of participation and request for a hearing (see DATES and ADDRESSES) and (2) the data, information, and analyses relied on to demonstrate that there is a genuine and substantial issue of fact that requires a hearing (see DATES and ADDRESSES). Any other interested person may also submit comments on this notice. Procedures and requirements governing this NOOH, a notice of appearance and request for a hearing, submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of a hearing, are contained in § 514.200 (21 CFR 514.200) and 21 CFR part 12.

The failure of a holder of an approval to timely file a request for a hearing as required by § 514.200 constitutes an election by the holder not to avail itself of the opportunity for a hearing and constitutes a waiver of any contentions concerning the legal status of any such drug product, and the Director of CVM will summarily enter a final order withdrawing the approvals. Any new animal drug product marketed without an approved NADA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for hearing that there is no genuine and substantial issue of fact that precludes the withdrawal of approval of the applications, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the person who requests a hearing, making findings and conclusions, and denying a hearing. If a hearing is requested and is justified by the sponsor’s response to this NOOH, the issues will be defined,
a presiding officer will be assigned, and a written notice of the time and place at which the hearing will commence will be issued as soon as practicable.

This notice is issued under section 512 of the FD&C Act and under the authority delegated to the Deputy Commissioner for Policy, Legislation, and International Affairs, Office of Policy, Legislation, and International Affairs.

V. Environmental Impact

The Agency has determined under 21 CFR 25.33(g) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. References

The following references are on display in the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they are also available electronically at https://www.regulations.gov. Although FDA verified the website addresses in this document, please note that websites are subject to change over time.


Dated: November 1, 2023.

Kimberlee Trzeciak,
Deputy Commissioner for Policy, Legislation, and International Affairs.

[FR Doc. 2023–24547 Filed 11–6–23; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2020–N–0955]

Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method

AGENCY: Food and Drug Administration, HHS.

ACTION: Final order.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final order to revoke the approved method for detecting residues of carbadox, a carcinogenic new animal drug used in swine feed. An approved method is required by the Federal Food, Drug, and Cosmetic Act (FD&C Act), as implemented by regulation, to show that no residue of carcinogenic concern from a new animal drug persists in any edible tissue or in any food derived from treated animals. The approved method measures quinoxaline-2-carboxylic acid (QCA) as a marker residue to detect the presence of any residue of carcinogenic concern. QCA is a metabolite of carbadox that FDA has judged does not present a carcinogenic risk. FDA is revoking the approved method for carbadox based on its determination that the method is inadequate to monitor the residue of carcinogenic concern in compliance with FDA’s operational definition of no residue (§ 500.82(b)(21 CFR § 500.82(b)(defining ‘no residue’; § 500.84(c)(3) (21 CFR 500.84(c)(3))). That is because the sponsor has not established the relationship between the concentration of the marker residue QCA and the concentration of the residue of carcinogenic concern.

On March 10, 2022, FDA held a public hearing under 21 CFR part 15, entitled, “Scientific Data and Information Related to the Residue of Carcinogenic Concern for the New Animal Drug Carbadox” to gather additional data and information. When FDA announced the hearing (87 FR 2093, January 13, 2022; https://www.fda.gov/animal-veterinary/workshops-conferences-meetings/part-15-public-hearing-scientific-data-and-information-related-residue-carcinogenic-concern-new), we requested public comments and presentations at the public hearing, particularly: (1) on data to inform our knowledge of the residue of carcinogenic concern not summarized in the FOI Summary for the 1998 supplemental approvals, including additional data regarding the fraction of noncarcinogenic residues in the total radiolabeled residues of carbadox; (2) for any given concentration of a marker residue, the corresponding

1 See § 500.82(b)(defining ‘marker residue’ as the residue whose concentration is in a known relationship to the concentration of the residue of carcinogenic concern in the last tissue to deplete to the S<sub>n</sub> and defining “S<sub>n</sub>” as the concentration of a residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer).

2 Consistent with FDA regulations, CVMTreats unidentified residues of a carcinogenic drug as carcinogenic. See § 500.82(b) (defining ‘residue of carcinogenic concern’ as all compounds in the total residue of a demonstrated carcinogen excluding any compounds judged by FDA not to present a carcinogenic risk).