withdraw approval of the new animal drug applications (NADAs) for carbadox. That proposed action was based on two grounds. First, 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. The DES Proviso exception allows such an animal drug to be approved if, among other things, no residue of such drug will be found by methods of examination prescribed or approved by the Secretary of Health and Human Services by regulations, in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animals. Second, new evidence demonstrates that carbadox is not shown to be safe under the General Safety Clause (section 512(e)(1)(B) of the FD&C Act). FDA has reviewed information submitted by the drug sponsor, including some studies submitted in response to the April 2016 NOOH, and determined that the current approved method for detecting residues of carcinogenic concern does not meet the requirements of part 500, subpart E (21 CFR part 500, subpart E), to demonstrate that there is ''no residue'' of carbadox in any food derived by treated animals as required by section 512(d)(1)(I) of the FD&C Act.

FDA is withdrawing the April 2016 NOOH, which proposed to withdraw the approved uses of carbadox. Elsewhere in this issue of the **Federal Register**, FDA is publishing a proposed order that, if finalized, will revoke the current approved method for carbadox that measures quinoxaline-2-carboxylic acid as the marker residue for carbadox. The proposed order is based on the inadequacy of the current approved method to monitor residue of carcinogenic concern in compliance with FDA's operational definition of ''no residue'' in part 500, subpart E, and the requirements in section 512(d)(1)(I) of the FD&C Act. If the proposed order to revoke the current approved method is finalized and the approved analytical method is revoked, we intend to publish in the **Federal Register** an NOOH proposing to withdraw all new animal drug applications for use of carbadox based on the lack of an approved method to demonstrate compliance with part 500, subpart E, and section 512(d)(1)(I) of the FD&C Act.

Dated: July 9, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2020–15245 Filed 7–17–20; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2016–N–0832]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed order.

SUMMARY: The Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM), is proposing an 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 currently approved method measures quinoxaline-2-carboxylic acid (QCA) as a marker residue to detect the presence of any residue of carcinogenic concern. CVM is proposing to revoke the approved method for carbadox based on our determination that it is inadequate to monitor residue of carcinogenic concern in compliance with FDA's operational definition of no residue because there is no established relationship between QCA measured by the approved method and the residue of carcinogenic concern.

DATES: Submit either electronic or written comments on the proposed order by September 18, 2020.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before September 18, 2020. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of September 18, 2020. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

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 posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions'').

Written/Paper Submissions

Submit written/paper submissions as follows:

- *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–2016–N–0832 for ''Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Revocation of Approved Method.'' 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.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. 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 comments. 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.* Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.*

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 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, *diane.heinz@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

I. Introduction

CVM is proposing to revoke the current approved method [1] used to determine whether residues of carcinogenic concern of carbadox are present. That method measures QCA as the marker residue for the residue of carcinogenic concern. CVM is proposing to revoke the method because it does not adequately monitor the residue of carcinogenic concern in compliance with FDA's operational definition of no residue. See § 500.84(c)(3) (21 CFR 500.84(c)(3)).

The Delaney Clause of the FD&C Act generally prohibits the approval of carcinogenic animal drugs unless an exception applies. See section 512(d)(1)(I) of the FD&C Act (21 U.S.C. 360b(d)(1)(I)). Under the ''Diethylstilbestrol (DES) Proviso'' exception, a carcinogenic new animal drug may be approved if, among other things, no residue of such drug will be found by methods of examination prescribed or approved by the Secretary of Health and Human Services (HHS) by regulations in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals. FDA's sensitivity of the method regulations (''SOM regulations'') establish the requirements for satisfying the DES Proviso (part 500, subpart E (21 CFR part 500, subpart E)). The regulations require, among other things, approval of a ''regulatory method'' to ensure that no residue of a carcinogenic drug will be found in edible portions of animals (§ 500.88 (21 CFR 500.88)).

When CVM approved the current regulatory method for carbadox in 1998, our understanding of carbadox metabolism, based on the data available at the time, led us to conclude that the safety of carbadox residues could be assured by tracking the non-carcinogenic residue QCA alone. As a result, CVM did not direct the sponsor to submit a proposed regulatory method that complied with § 500.88. Instead, CVM set a ''tolerance'' for QCA based on our conclusion that carcinogenic residues, including desoxycarbadox (DCBX), a known carcinogenic metabolite of carbadox, depleted quickly (within 72 hours) while QCA residues depleted more slowly. However, CVM has reevaluated the current approved method because we have concluded, based on subsequent studies, that carcinogenic residues persist longer than previously known. In its reevaluation of the current approved method, CVM has determined that the current approved method cannot adequately monitor residue of carcinogenic concern because there is no established relationship between QCA and the residue of carcinogenic concern. That means that determining the concentration of QCA in animal tissue does not allow CVM to conclusively determine whether the residue of carcinogenic concern remains in the tissue. Thus, the current approved method does not comply with part 500, subpart E, and therefore does not satisfy the statutory requirement of section 512(d)(1)(I) of the FD&C Act. The importance of addressing the inadequacies of the current approved method is underscored by the new data that suggest that residues of carcinogenic concern of carbadox do not deplete in animal tissue as quickly as previously believed. As a result, we are proposing to revoke the currently approved method.

If this proposed order to revoke the current approved method is finalized and this method is revoked, we intend to publish in the **Federal Register** a notice of opportunity for hearing (NOOH) proposing to withdraw approval of all new animal drug applications for use of carbadox based on the lack of an approved method for measuring residues as required by part 500, subpart E. See section 512(d)(1)(I) of the FD&C Act. Elsewhere in this issue of the **Federal Register**, FDA is withdrawing the April 12, 2016, NOOH [2] (81 FR 21559) for its proposal to withdraw approval of all new animal drug applications for use of carbadox in medicated swine feed. (A correction to the April 12, 2016, NOOH was published in the **Federal Register** on April 21, 2016 (81 FR 23499).)

II. Background

A. Regulation of Carcinogenic New Animal Drugs

Under the Delaney Clause of the FD&C Act, FDA generally cannot approve a new animal drug application (NADA) if the drug that is the subject of that application induces cancer in humans or animals (section 512(d)(1)(I) of the FD&C Act). An exception to this general rule is commonly known as the ''DES Proviso,'' [3] which allows for the approval of a carcinogenic new animal drug where CVM 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) of the FD&C Act).

As part of an NADA, CVM requires that the sponsor include a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of this drug will be safe (§ 514.1(b)(7) (21 CFR

[1] The current approved method, ''Determination of Carbadox as Quinoxaline-2-carboxylic Residues in Swine Liver and Muscle Tissues after Drug Withdrawal,'' is available at *https://www.fda.gov/media/136267/download.*

[2] See *https://www.federalregister.gov/documents/2016/04/12/2016-08327/phibro-animal-health-corp-carbadox-in-medicated-swine-feed-opportunity-for-hearing.*

[3] The ''DES Proviso'' refers to Diethylstilbestrol, a carcinogenic hormone widely used in beef-cattle feed at the time the Delaney Clause was enacted.

514.1(b)(7))). Carcinogenic drugs, such as carbadox, must also meet the requirements in part 500, subpart E (§ 514.1(b)(7)(ii)). These SOM regulations set out the requirements for demonstrating that no residues of the drug will be found by an approved regulatory method in any edible tissues of or in any foods obtained from the animal, as required to comply with the DES Proviso.

Specifically, the SOM regulations require CVM to determine if any animal drug or any of its metabolites is a carcinogen (§ 500.84(a)). For the drug and each metabolite that FDA decides should be regulated as a carcinogen,[4] CVM calculates, based on submitted assays, the concentration of the test compound in the total diet of the test animal that corresponds to a maximum lifetime risk of cancer in the test animal of 1 in 1 million (§ 500.84(c)(1)). CVM designates the lowest concentration (*i.e.,* the concentration of the most potent carcinogen) thus calculated as the S_o (§ 500.84(c)(1)). The S_o corresponds to a concentration of residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to people (§ 500.82(b) (21 CFR 500.82(b))). The residue of carcinogenic concern includes all compounds in the total residue of a demonstrated carcinogen excluding any compounds determined by CVM not to present a carcinogenic risk (§ 500.82(b)). CVM treats unidentified residues of a carcinogenic drug as carcinogenic (§ 500.82(b) (definition of ''Residue of carcinogenic concern'')). Because FDA relies on the S_o from the most potent carcinogen, this approach ensures that use of the drug does not present a significant increase in the risk of cancer when considering all residues in edible tissues.

Because the total human diet is not derived only from food-producing animals, the SOM regulations make adjustments for human food intake of edible tissues and determine the concentration of residue of carcinogenic concern in a specific edible tissue (such as muscle, liver, kidney, milk, or eggs) that corresponds to no significant increase in the risk of cancer to the human consumer. CVM assumes for purposes of these regulations that this value will correspond to the concentration of residues in a specific edible tissue that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million. This value is designated as the S_m (§§ 500.82(b) and 500.84(c)(1)). By limiting concentration of residue of carcinogenic concern to a value at or below the S_m, a consumer can eat a specific edible tissue every day for an entire lifetime without increasing his or her cancer risk by more than 1 in 1 million.

Based on data submitted by a sponsor, CVM selects a target tissue (the edible tissue selected to monitor for residues in the target animals) and a marker residue [5] and designates the concentration of the marker residue that the regulatory method must be able to detect in the target tissue (§ 500.86(a) through (c) (21 CFR 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, that ensures that the residue of carcinogenic concern does not exceed S_m in each of the edible tissues when the marker residue is not detectable (§§ 500.82(b) and 500.86(c)). When the marker residue is at or below the R_m, the residue of carcinogenic concern in the human diet does not exceed S_o (§ 500.86(c)).

A sponsor must submit a regulatory method that is able to detect the marker residue at or below the R_m (§§ 500.88(b) and 500.84(c)(2) (the Limit of Detection (LOD) for the regulatory method must be less than or equal to R_m.)). Under the SOM regulations, a method must be able to confirm the identity of the marker residue in the target tissue at a minimum concentration corresponding to the R_m. FDA will determine the LOD from the submitted analytical method validation data (§ 500.88(b)).[6] If a method cannot be 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. See 21 U.S.C. 360b(d)(1)(I); § 500.88.

B. History of Carbadox Approvals

Currently, there are three approved NADAs for use of carbadox in medicated swine feed, either alone or in combination with other approved new animal drugs. Carbadox, a quinoxaline derivative, is a synthetic antimicrobial used to manufacture medicated feeds that are administered ad libitum to swine. Phibro Animal Health Corp. (Phibro), GlenPointe Centre East, 3d Floor, 300 Frank W Burr Blvd., Suite 21, Teaneck, NJ 07666, is currently the sponsor of all three approved NADAs.

1. NADA 041–061

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 at the rate of 10 to 25 grams per ton (g/ton) of feed for increased rate of weight gain and improved feed efficiency; and at 50 g/ton of feed for control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery), control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *Salmonella choleraesuis*), and for increased rate of weight gain and improved feed efficiency. Currently, the withdrawal period for these uses of carbadox is 42 days (§ 558.115(d)(1)(ii) and (d)(2)(ii) (21 CFR 558.115(d)(1)(ii) and (d)(2)(ii))).

In January 1998, FDA approved a supplemental application to NADA 041–061. Based on the review of the data submitted in support of this supplemental application, CVM concluded: (1) The parent compound carbadox is rapidly metabolized and carcinogenic residues of the drug do not persist in any edible tissues beyond 72 hours postdosing; (2) unextracted residues of carbadox are noncarcinogenic residues related to the noncarcinogenic metabolite QCA; (3) extractable QCA is the only residue detectable in the edible tissues 72 hours postdosing; and (4) thus QCA is a reliable marker residue for carbadox and its metabolites.[7] Despite the requirement in § 500.86 that an R_m, instead of a tolerance, be established for a carcinogenic drug, CVM assigned a ''tolerance of 30 ppb [parts per billion] for QCA in swine liver'' as a means of

[4] 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).

[5] The marker residue is 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_m (§ 500.82(b)).

[6] As discussed above, the Delaney Clause prohibits the use of carcinogenic animal drugs unless an exception, such as the DES Proviso, applies. See section 512(d)(1)(I) of the FD&C Act. The DES Proviso requires that, among other things, no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary of HHS by regulations) in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals. FDA's SOM regulations establish the process by which a carcinogenic new animal drug may satisfy the DES Proviso. The SOM regulations were revised in 2002 to delete the operational definition of the term ''no residue'' and to make conforming amendments to other parts of the regulations. The LOD of the method replaced the R_m as the ''no residue'' determinant.

[7] FDA, Freedom of Information (FOI) Summary, NADA 041–061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval January 30, 1998. Available at *https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/308.*

''assur[ing] that all residues of carcinogenic concern are well below their respective S_o in all edible tissues'' [8] because, based on the conclusions listed above, CVM believed, at the time of the 1998 supplemental approvals, that a tolerance would adequately protect public health. For a ''Regulatory Method,'' CVM approved a method that used a ''gas chromatographic assay with electron capture detection.'' [9] However, this method was not published in the **Federal Register** as provided in § 500.88, and the method that had been published for the 1972 approval was removed from the Code of Federal Regulations. Nevertheless, since the January 1998 approval of the supplemental NADA, CVM and the sponsor have treated the current approved method as the method of examination prescribed or approved by the Secretary of HHS by regulations for purposes of applying section 512(d)(1)(I) of the FD&C Act, the Delaney Clause, to carbadox.

In October 1998, FDA approved an additional supplemental NADA for NADA 041–061, changing the withdrawal period for carbadox medicated feeds from 70 days to 42 days. This supplemental NADA was approved based on the previous approval of a tolerance of 30 parts per ppb for QCA and a residue depletion study using the approved QCA analytical method that showed residues of QCA in liver depleted below 30 ppb by 42 days.[10]

2. NADA 092–955

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 at 50 g/ton of feed plus pyrantel tartrate at 96 g/ton of feed for control of swine dysentery (vibrionic dysentery, bloody scours, or hemorrhagic dysentery), control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by *S. choleraesuis*), as an aid in the prevention of migration and establishment of large roundworm (*Ascaris suum*) infections, and as an aid in the prevention of establishment of nodular worm (*Oesophagostomum*) infections. The withdrawal period for the use of this drug combination is 70 days (§ 558.115(d)(3)(ii)).

3. NADA 141–211

NADA 141–211, originally approved in 2004 (69 FR 51173, August 18, 2004), provides for the use of MECADOX 10 (carbadox) Type A medicated article with TERRAMYCIN 50, TERRAMYCIN 100, or TERRAMYCIN 200 (oxytetracycline) Type A medicated articles to manufacture two-way, combination drug Type C medicated swine feeds at 10 to 25 g/ton of feed plus oxytetracycline at levels in feed to deliver 10 mg carbadox 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)(ii)).

C. Post-Approval Information Regarding Carcinogenic Residues

After the 1998 supplemental approval, FDA has subsequently evaluated data regarding the persistence of carbadox residues in swine treated with carbadox, including residues of carbadox, DCBX, and QCA. Based on a review of this data, FDA has concluded that: (1) Carcinogenic residues persist in animal tissue more than 72 hours postdosing and (2) QCA is not the only residue detectable in animal tissue after 72 hours postdosing.

For the 2003 Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) meeting, the sponsor provided data in which it reported that DCBX is measurable quantitatively (in specific amounts) at 15 days postdosing (the last sampling timepoint in the study) (Ref. 1). Based on those studies, which showed the persistence of genotoxic, carcinogenic residues, JECFA could not determine an amount of residues of carbadox in human food that would have no adverse health effects in consumers. Following that meeting, the Codex Committee on Residues of Veterinary Drugs in Foods withdrew the maximum residue levels for carbadox, and carbadox has been removed from the market in many foreign jurisdictions, including the European Union (Ref. 2), Canada (Ref. 3), and Australia (Ref. 4).

Pursuant to section 512(*l*)(1) of the FD&C Act, FDA ordered Phibro to provide it with data related to the persistence of DCBX in edible tissues and the appropriateness of QCA as a marker residue. Phibro responded, among other submissions, with the same data provided to the 2003 JECFA. CVM reviewed the 2003 JECFA data and determined that the data show qualitatively (in non-specific amounts) that carbadox and DCBX are present in liver tissue samples at 48 hours and at 15 days withdrawal, respectively. CVM concluded that the mass spectrometry chromatograms and the reported DCBX concentration data provide qualitative confirmation of the presence of DCBX at 15 days withdrawal in the samples exposed to digestive enzymes.

CVM has also reviewed data submitted by the sponsor, including data from a 2008 study discussed in its Request for a Hearing in response to the 2016 NOOH and studies it submitted in July 2016. In general, proprietary data (such as the 2008 and 2016 studies conducted by Phibro) are considered confidential commercial information and therefore cannot be shared publicly in this proposed order. Based on its review of these data, CVM concluded that the known carcinogenic residues (carbadox and DCBX) persist beyond 72 hours and that QCA is not the only residue detectable after 72 hours. Furthermore, the sponsor has not provided data to establish a relationship between QCA and the residue of carcinogenic concern, which include carbadox and DCBX, nor have they provided data to establish the residue level of QCA at which the residue of carcinogenic concern in the diet of people represents no significant increase in the risk of cancer to people. Without these data, CVM cannot establish the R_m and the sponsor cannot demonstrate ''no residue'' of carcinogenic concern as required by the SOM regulations in part 500, subpart E, as implementing the FD&C Act at 21 U.S.C. 360b(d)(1)(I).

D. Statutory Authority To Propose Order

Under 5 U.S.C. 554(e) (section 5(d) of the Administrative Procedure Act (APA)), an agency, in its sound discretion, may issue a declaratory order to terminate a controversy or remove uncertainty. The APA defines ''order'' as the whole or a part of a final disposition, whether affirmative, negative, injunctive, or declaratory in form, of an agency in a matter other than rulemaking but including licensing (5 U.S.C. 551(6)). The APA defines ''adjudication'' as agency process for the formulation of an order (5 U.S.C. 551(7)). FDA's regulations, consistent with the APA, define ''order'' to mean the final agency disposition, other than

[8] Id. at 13.

[9] Id.

[10] FDA, FOI Summary, NADA 041–061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval October 5, 1998. Available at *https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/1673.*

the issuance of a regulation, in a proceeding concerning any matter (§ 10.3(a) (21 CFR 10.3(a)). Our regulations also define ''proceeding and administrative proceeding'' to mean any undertaking to issue, amend, or revoke a regulation or order, or to take or not to take any other form of administrative action, under the laws administered by FDA (§ 10.3(a)). Moreover, our regulations establish that the Commissioner of Food and Drugs may initiate an administrative proceeding to issue, amend, or revoke an order (21 CFR 10.25(b)).

On our own initiative, we are proposing to formulate a 5 U.S.C. 554(e) declaratory order to remove uncertainty regarding the approved method for carbadox that measures QCA as a marker residue. An order is the most appropriate method to revoke the approved method because there is no rule to amend. The current approved method is not currently published in the **Federal Register**, contrary to § 500.88, and the method that had been published for the 1972 approval was removed from the Code of Federal Regulations in 1998. The FD&C Act does not provide the procedure we must use to determine whether a method of examination that was never published in regulation satisfies the regulatory requirements of part 500, subpart E. Thus, we are choosing to issue a declaratory order to remove uncertainty.

III. Discussion

CVM proposes to revoke the approved method for carbadox that measures QCA as the marker residue. The currently approved method cannot adequately monitor residue of carcinogenic concern because there is no established relationship between QCA and the residue of carcinogenic concern. Thus, the current approved method does not comply with part 500, subpart E, and therefore does not satisfy the statutory requirement of section 512(d)(1)(I) of the FD&C Act.

When CVM approved a supplemental NADA for carbadox in 1998, it did not require the sponsor to provide data establishing a known relationship between the concentration of the marker residue (QCA) and the concentration of the residue of carcinogenic concern (§ 500.86(a) through (c)). At the time of the 1998 supplemental NADA approval, CVM did not believe that such information was necessary because of previous conclusions that it had made about the persistence of carcinogenic residue in the edible tissues of animals dosed with carbadox. Results from subsequent studies have led CVM to reexamine the conclusions made in 1998. CVM concludes, based on data from these studies, that it is necessary to establish a known relationship between the marker residue and the residue of carcinogenic concern, as required by regulation. Accordingly, CVM is proposing to revoke the current approved method because it is inadequate to monitor the residue of carcinogenic concern.

A. CVM's Conclusions in the January 1998 Approval

In reviewing residue chemistry information for the supplemental NADA for carbadox in January 1998, CVM relied on studies conducted by the sponsor[11] and academic researchers[12] to establish an S_o and an S_m for the most potent of the carcinogenic compounds. As part of the supplemental NADA, the sponsor submitted toxicology studies, including carcinogenicity bioassays with carbadox, DCBX, and hydrazine (another carcinogenic metabolite of carbadox).[13] These studies indicated that DCBX was the most potent of the three identified carcinogenic residues of carbadox.[14] Based on the carcinogenicity of DCBX, CVM calculated an S_o of 0.061 ppb for total residue of carcinogenic concern for carbadox in the total diet. CVM calculated an S_m value for the residue of carcinogenic concern in muscle at 0.305 ppb, in liver at 0.915 ppb, and in kidney and fat at 1.830 ppb.[15]

Based on information submitted as part of the supplemental NADA approved in January 1998, CVM made conclusions about how long carcinogenic residues persist in the edible tissues of swine after treatment with carbadox and about the appropriate marker residue to select to monitor carbadox use. As stated in the FOI summary for the January 1998 approval of the supplemental NADA,[16] CVM concluded the data:

Show that carbadox, desoxycarbadox and hydrazine do not persist in edible tissue as detectable residues beyond 72 hours. The agency's evaluation of these data, and the new information provided by the sponsor, demonstrate that following administration, parent carbadox is rapidly metabolized; that the metabolism of carbadox is similar among species; that the *in vivo* metabolism of the compounds of carcinogenic concern is also rapid and irreversible such that the resulting metabolic products cannot regenerate compounds of carcinogenic concern; that the unextractable residues are related to non-carcinogenic compounds, quinoxaline-2-carboxylic acid (QCA) and quinoxaline-2-carboxaldehyde; and that QCA is the only residue detectable in the edible tissues beyond 72 hours post dosing. Thus, the agency concludes that the unextractable bound residue is not of carcinogenic concern and that QCA is a reliable marker residue for carbadox.

CVM made the following conclusions during the review of the supplemental NADA for carbadox approved in January 1998:

1. Carcinogenic residues do not persist in animal tissue beyond 72 hours postdosing.
2. Extractable QCA is the only residue detectable in edible tissues 72 hours postdosing.
3. Unextractable residues are noncarcinogenic residues related to QCA.
4. QCA is a reliable marker residue for carbadox and its metabolites.
5. No residue of carcinogenic concern, even below the S_o, is detectable by any method after 72-hours postdosing.

Because of these conclusions, CVM did not require the sponsor to submit data to meet the requirements of the part 500, subpart E regulations despite the fact that carbadox is a carcinogen. These regulations require CVM to designate an R_m (the residue level at which the residue of carcinogenic concern in the diet of people represents no significant increase in the risk of cancer to people) based on a known relationship between the marker residue and the residue of carcinogenic concern. In addition, the sponsor must provide a regulatory method that can detect the marker residue at or below the R_m.[17] CVM

[11] Pfizer, Inc. was the sponsor for carbadox until 2001. The current sponsor is Phibro Animal Health.

[12] Summaries of these studies can be found in the FDA FOI Summary, NADA 041–061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval January 30, 1998, available at *https://animaldrugsatfda.fda.gov/adafda/app/search/public/document/downloadFoi/308;* and, in the 1990 evaluation of carbadox by the Joint FAO/WHO Expert Committee on Food Additives, available at *http://www.fao.org/fileadmin/user_upload/vetdrug/docs/41-3-carbadox.pdf* (accessed on October 11, 2019).

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

[14] Id.

[15] Id.

[16] Id.

[17] Under § 500.86, the necessary steps to meet the operational definition of ''no residue'' are: (1) Measure the depletion of the residue of carcinogenic concern until its concentration is at or below the S_m (0.915 ppb) in liver; (2) measure the depletion of the marker residue until the concentration of the residue of carcinogenic concern is at or below the S_m; (3) use the information in (1) and (2) to establish an R_m; and, (4) according to the regulations as they existed in 1998, develop a method that could detect the marker residue of the drug, as long as the marker residue would only be detected at or below the R_m under the proposed conditions of use. According to

Continued

instead established a tolerance of 30 ppb for QCA, and granted the supplemental approval for carbadox. Subsequent to the 1998 supplemental approval, CVM has evaluated additional information that undermines its previous conclusions that carcinogenic residues deplete within 72 hours and that QCA is the only residue detectable at 72 hours postdosing. These new data reinforce the inadequacy of the currently approved method and clarify the need for a method that satisfies the requirements of part 500. See, supra, Section II.C.

B. The Current Approved Method for Carbadox That Measures QCA as the Marker Residue for Carbadox Is Inadequate

Under section 512(d)(1)(I) of the FD&C Act, carcinogenic new animal drugs, such as carbadox, must have a method of detection, prescribed or approved by regulation, to ensure that no residue of carcinogenic concern persists in any edible tissue or other food derived from a treated animal. CVM has implemented this statutory requirement through its SOM regulations in part 500, subpart E, which require that each carcinogenic new animal drug have a marker residue with a known relationship to the residue of carcinogenic concern. This relationship is necessary to establish a concentration of the marker residue (the R_m) that ensures any residue of carcinogenic concern in a specific edible tissue is below the level corresponding to maximum lifetime risk of cancer in the test animal of 1 in 1 million (the S_m), based on calculations that consider the entire diet (the S_o). The approved method must have a limit of detection less than or equal to the R_m.

Although CVM approved the current method for carbadox as part of the supplemental NADA in January 1998 and designated the S_m and S_o, we did not require the sponsor to provide data showing the relationship between QCA and the residue of carcinogenic concern and therefore did not designate an R_m. Nor did we require the sponsor to identify a regulatory method with a limit of detection less than or equal to the R_m. Without 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 the S_m and S_o at the established withdrawal period. Accordingly, it is impossible, based on information currently available, to use the current approved method to ensure compliance with the operational definition of no residue.

Furthermore, based on studies conducted since 1998, CVM has reevaluated the conclusions that originally led us to determine that assignment of a tolerance of 30 ppb for QCA in swine liver would assure that the residue of carcinogenic concern would remain below their respective S_o in all edible tissues. CVM concludes, based on its review of the data, that carcinogenic residues persist longer than previously known. Because there is no regulatory method that detects when the residue of carcinogenic concern falls below the limit of detection for the R_m, the current approved method is inadequate for monitoring compliance with FDA's operational definition of no residue. See § 500.84(c)(3). Accordingly, the approved method for carbadox does not satisfy the statutory or regulatory requirements.

IV. Conclusion

In the January 1998 approval of the supplemental NADA for carbadox, CVM previously determined that carbadox and its metabolites, including DCBX, induce cancer in animals but that no such residues of the drug would be found in edible tissues after the preslaughter withdrawal period by the approved regulatory methods of examination. However, the failure to establish an R_m or a relationship between QCA residues and residue of carcinogenic concern in animal tissue during the 1998 process leads CVM to now conclude that the current approved method does not meet the requirements of the FD&C Act and the SOM regulations and is inadequate to monitor carbadox residues in compliance with FDA's operational definition of no residue. New information available to CVM since the approval of the January 1998 supplemental NADA reinforces the importance of having an approved regulatory method that complies with the SOM regulations. Therefore, we are proposing to revoke the current approved method.

V. References

The following references are on display at 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.* FDA has verified the website addresses, as of the date this document publishes in the **Federal Register**, but websites are subject to change over time.

1. Suárez, A.F. and Arnold, D., Addendum to the carbadox monograph prepared by the 36th meeting of the Committee and published in the FAO Food and Nutrition Paper 41/3, Rome 1991. Available at: *http://www.fao.org/fileadmin/user_upload/vetdrug/docs/41-15-carbadox.pdf* (accessed on April 7, 2020).
2. Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Carbadox. Available at: *https://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=2176* (accessed on April 7, 2020).
3. Internet Archive of Health Canada, Drug and Health Products (June 2008), *https://web.archive.org/web/20080609050022/http://www.hc-sc.gc.ca/dhp-mps/vet/faq/faq_mrl-lmr-eng.php* (accessed on April 7, 2020).
4. Australian Pesticides and Veterinary Medicines Authority, ''Substances not permitted for use on food-producing animals in Australia,'' *https://apvma.gov.au/node/11626* (accessed on April 7, 2020).

Dated: July 9, 2020.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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the current regulations, step (4) requires the development of a method that complies with the operational definition of no residue (the method's LOD is less than or equal to the R_m).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

[Document Identifier OS–0990–0278]

Agency Information Collection Request. 30-Day Public Comment Request

AGENCY: Office of the Secretary, HHS.

ACTION: Notice.

SUMMARY: In compliance with the requirement of the Paperwork Reduction Act of 1995, the Office of the Secretary (OS), Department of Health and Human Services, is publishing the following summary of a proposed collection for public comment.

DATES: Comments on the ICR must be received on or before August 19, 2020.

ADDRESSES: Written comments and recommendations for the proposed information collection should be sent within 30 days of publication of this notice to *www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under 30-day Review—Open for Public Comments'' or by using the search function.

FOR FURTHER INFORMATION CONTACT: Sherrette Funn, *Sherrette.Funn@hhs.gov* or (202) 795–7714. When submitting