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; Opportunity for Hearing

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of opportunity for hearing.

SUMMARY: The Food and Drug Administration (FDA), 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. This action is based on CVM's determination that the use of carbadox under the approved conditions of use results in residues of carcinogenic concern in the edible tissues of the treated swine.

DATES: Phibro Animal Health Corp. may submit a request for a hearing by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. Submit all data and analysis upon which the request for a hearing relies by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

ADDRESSES: The request for a hearing may be submitted by Phibro Animal Health Corp. by either of the following methods:

Electronic Submission

- Federal eRulemaking Portal: http://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 http://www.regulations.gov will be posted to the docket unchanged.

Written/Paper Submission

- Mail/Hand delivery/Courier (for written/paper request for a hearing): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Because your request for a hearing will be made public, you are solely responsible for ensuring that your request does not include any confidential information that you 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-2016-N-0832 for "Phibro Animal Health Corp.; Carbadox in Medicated Swine Feed; Opportunity for Hearing." The request for a hearing will be placed in the docket and publicly viewable at http://www.regulations.gov or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

Phibro Animal Health Corp. may submit all data and analysis 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 analysis. 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 http://www.regulations.gov or available at the Division of Dockets Management

between 9 a.m. and 4 p.m., Monday through Friday. Submit both copies to the Division of Dockets Management. 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 you may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: http://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to http://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 http://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): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Division of Dockets Management, 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; Opportunity for Hearing." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at http://www.regulations.gov or at the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

- 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 http://www.regulations.gov. Submit both copies to the Division of Dockets Management. 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: http://www.fda.gov/regulatoryinformation/dockets/default.htm.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to http://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 Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Vernon Toelle, Center for Veterinary Medicine (HFV-230), 7519 Standish Pl., Rockville, MD 20855, 240-276-9200.

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. (Phibro), 65 Challenger Rd., Ridgefield Park, NJ 07660, 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 to swine. Carbadox is indicated for the control of dysentery and bacterial enteritis, and for growth promotion. A tolerance of 30 parts

per billion (ppb)[1] has been established for residues of quinoxaline-2-carboxylic acid (QCA), the marker residue, in liver of swine (21 CFR 556.100).

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

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:

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

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))).

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:

- Carbadox 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); for control of bacterial swine enteritis (salmonellosis or necrotic enteritis caused by Salmonella

[1]For consistency and readability throughout this document, concentrations are reported as parts per billion even though original references may report some concentrations as parts per trillion (ppt).

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)).

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 for the following conditions of use:

- Carbadox 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)).

II. Basis for Withdrawal of Approval

CVM is providing notice of an opportunity for a hearing (NOOH) on a proposal to withdraw approval of the NADAs providing for use of carbadox in medicated swine feeds. New evidence regarding carcinogenic residues in edible tissues of swine treated with carbadox raises serious questions about the human food safety of the drug. Grounds for withdrawing carbadox are twofold. First, new evidence demonstrates that the Delaney Clause in section 512(d) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 360b), 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.C). 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).

During the review of a supplemental application to NADA 041-061 approved in January 1998, CVM made the following conclusions about the drug: (1) The parent compound carbadox is rapidly metabolized and carcinogenic residues of the drug are not identifiable in any edible tissues beyond 72 hours post dosing; (2) remaining unextracted residues of carbadox are noncarcinogenic residues related to the noncarcinogenic metabolite QCA; and (3) QCA is a reliable marker residue for carbadox and its metabolites (Ref. 1).

Since the evaluation of information submitted by the sponsor in that supplemental application, CVM has become aware of new information that calls into question the basis for its previous conclusions. As described more fully in Section V., this includes new residue depletion data presented to the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[2] in 2003 that shows that when the marker residue QCA reaches the approved tolerance of 30 ppb in liver, concentrations of the carcinogen desoxycarbadox (DCBX) in the liver would be approximately 4 times higher than the concentration that would be considered safe (Ref. 2 at pp. 16-17). In addition, the new residue depletion data presented to JECFA in 2003 call into question CVM's previously held conclusion that the unextracted residues of carbadox at the withdrawal period are noncarcinogenic compounds related to the QCA metabolite (Ref. 1). The Agency treats the

[2]JECFA is an independent committee of international scientific experts administered jointly by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) for the purpose of providing independent scientific advice to the FAO, WHO, and member countries. It has been meeting since 1956 specifically to evaluate the safety of food additives, including the animal drug residues in edible tissues. See http://www.codexalimentarius.org/scientific-basis-for-codex/jecfa/en/ and http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/.

unidentified residues--metabolites of a carcinogenic parent drug with demonstrated carcinogenic metabolites--as carcinogenic. Therefore, the drug is not shown to be safe under the General Safety Clause and the Delaney Clause applies to the drug, because the DES Proviso exception is no longer met.

Continued approval of carbadox would expose humans to concentrations of total residues of carcinogenic concern that are approximately 30 times higher (for the approved 42-day withdrawal period) or 11 times higher (for the approved 70-day withdrawal period) than the 0.915 ppb concentration of total residues of carcinogenic concern in liver that would be considered safe (Ref. 3 at p. 17, Table 8). Moreover, the sponsor has not identified an appropriate marker and analytical method to assure that residues of carcinogenic concern are below the level at which the residues present in the total human diet present no significant increase in the risk of cancer to people (the S_o).

In addition to the new information presented to JECFA (Ref. 2), publications by Boison, et al., in 2009 (Ref. 4) and Baars, et al., in 1990 (Ref. 5) that were recently provided to CVM by the sponsor call into question the previous conclusion that QCA is an appropriate marker and that all residues of carcinogenic concern deplete within 72 hours after dosing.

The new evidence from the 2003 JECFA report (Ref. 2) in conjunction with the publications by Boison, et al., in 2009 (Ref. 4) and Baars, et al., in 1991 (Ref. 6), erode the scientific justification for, and validity of, conclusions previously made about the drug in 1998. Based on this new information, evaluated together with the information available at the time of the approvals, CVM has determined that the drug is not shown to be safe under the General Safety Clause and that the Delaney Clause applies to the drug, because the DES Proviso

exception is no longer met. Therefore, CVM proposes to withdraw approval of all NADAs for new animal drugs containing carbadox.

III. Legal Context of the Proposed Action and Grounds for Withdrawal

A. The Determination of Safety in Section 512

Carbadox, for each of its uses in swine, is a new animal drug as defined in section 201(v) of the FD&C Act (21 U.S.C. 321(v)). As such, under sections 301, 501, 512, 571, and 572 of the FD&C Act (21 U.S.C. 331, 351, 360b, 360ccc, 360ccc-1), the drug cannot be legally introduced or delivered for introduction into interstate commerce in the absence of an NADA approval, a conditional approval, or an animal drug indexing. The requirements for approval of an NADA are set out in section 512(d)(2)(A) of the FD&C Act. Section 512(b)(1)(A) of the FD&C Act requires that a new animal drug must be shown to be safe and effective for its intended uses. Section 201(u) of the FD&C Act provides that "safe" as used in section 512 of the FD&C Act "has reference to the health of man or animal." The determination of safety requires CVM to consider, among other relevant factors, "the probable consumption of such drug and any substance formed in or on food because of the use of such drug…" (section 512(d)(2)(A) of the FD&C Act). Accordingly, CVM must consider not only safety of the new animal drug to the target animal, but also the safety to humans of substances formed in or on food as a result of the use of the new animal drug.

"Safe," in the context of human food safety, means a "reasonable certainty of no harm." The definition is derived from language in H. Rep. No. 85-2284, at 4-5 (1958), defining the term "safe" as it appears in section 409 of the FD&C Act, which governs food additives (21 U.S.C. 348). Until passage of the Animal Drug Amendments of 1968 (Pub. L. 90-399) (the 1968 amendments), substances formed in or on food due to the use of animal drugs in food-producing

animals were regulated under the food additive provisions in section 409 of the FD&C Act. The 1968 amendments consolidated all of the existing statutory authorities related to animal drugs into section 512 of the FD&C Act, and the legislative history shows that the consolidation in no way changed the authorities with respect to the regulation of new animal drugs (S. Rep. No. 90-1308, at 1 (1968)). During the new animal drug application review process, CVM has consistently applied the "reasonable certainty of no harm" standard in determining the safety of substances formed in or on food as a result of the use of a new animal drug in a food-producing animal.

In order to determine whether a new animal drug meets this standard, section 512(b)(1)(G)-(H) of the FD&C Act requires that whenever a drug may result in residues of the drug or its metabolites in food, an application must include not only full reports of investigations to show that the use of the drug is safe, but also a description of practicable methods for monitoring food to assure that there are no unsafe residues in human food attributable to the drug use, and a demonstration that the conditions of use are adequate to assure there are no unsafe residues.

In sum, under section 512(d)(2) of the FD&C Act, the Agency is required, in the evaluation of the supporting safety data, among other things, to consider:

- The probable consumption of such drug and of any substance formed in or on food because of the use of such drug (i.e., probable human consumption of residues including the parent drug and its metabolites);
- The cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substance, i.e., toxicological effects of the compounds comprising the residues; and

- Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data (i.e., establishing "safe" levels of residues using appropriate safety factors to extrapolate animal data on cumulative effects to humans).

When establishing the human food safety of a noncarcinogenic new animal drug used in food-producing animals, CVM establishes a no observed effect level (NOEL) for the residues of that drug in edible tissues--namely, the highest dose of the drug that does not produce the most sensitive treatment-related toxic endpoint in test animals (Ref. 7). From the NOEL, CVM uses safety factors to calculate an acceptable daily intake, and consumption factors to calculate the safe concentration of residues in a particular edible tissue (Ref. 7 at p. 15; section 512(b)(1)(H) of the FD&C Act).

Carbadox is both a genotoxic[3] and mutagenic carcinogen in animals. In the case of a genotoxic carcinogenic drug, establishing the human food safety of the compound via a NOEL is not feasible, therefore human food safety of carcinogenic compounds is ordinarily evaluated by using linear, low-dose extrapolation to evaluate the maximum concentration of total residues of carcinogenic concern that can be present in the total human diet without a significant increase in the risk of cancer to the human consumer (section 512(d)(1)(I) of the FD&C Act; 21 CFR 500.82 and 500.84). In both cases, the safe residue level of the drug is determined through an evaluation of the relevant data relating to the three factors listed above; viz., the probable consumption of

[3]Genotoxic refers to chemicals that react with DNA or chromosomes to cause damage. When the damage is not repaired and the effect is a heritable change (cell to cell or parent to offspring), it is also termed mutagenic. Thus not all genotoxic chemicals are mutagenic, but all mutagenic chemicals are genotoxic. Uncorrected mutagenesis is thought to be a key step in the development of cancer. "Mechanisms of Toxicity," in Casarett & Doull's Toxicology: The Basic Science of Poisons, edited by Klassen, C. D., 8th Ed., pp. 49-123, 2013.

the drug residue and its cumulative effect as determined through all relevant safety factors (section 512(d)(2) of the FD&C Act).

B. Grounds for Withdrawal Under the FD&C Act

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 an approved application or not available to the Secretary of Health and Human Services 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 such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved or that subparagraph (I) of paragraph (1) of subsection (d) applies to such drug. The Secretary of Health and Human Services has delegated this authority to the Commissioner of Food and Drugs. See FDA Staff Manual Guide 1410.10 (April 11, 2014).

In other words, grounds for withdrawal exist where new evidence shows either that the Delaney Clause applies to the drug ("subparagraph (I) of paragraph (1) of subsection (d)") or that the drug is not shown to be safe under the approved conditions of use (the General Safety Clause). As explained further, new evidence demonstrates that carbadox meets both grounds for withdrawal.

In a proceeding to withdraw the approval of an NADA, the sponsor has the burden of proof to demonstrate that the product is safe and therefore that the NADA approval should remain in effect (21 CFR 12.87(d): ("At a hearing involving issuing, amending, or revoking a regulation or order relating to the safety or effectiveness of a drug…the participant who is contending that the product is safe or effective or both and who is…contesting withdrawal of

approval has the burden of proof in establishing safety or effectiveness or both and thus the right to approval."); (see also Rhone-Poulenc, Inc. v. FDA, 636 F.2d 750, 752 (D.C. Cir. 1980); Hess & Clark v. FDA, 495 F.2d 975, 992 (D.C. Cir. 1974)). Nevertheless, CVM bears an initial burden of showing that new evidence regarding the new animal drug raises serious questions about the safety of the new animal drug. See Rhone-Poulenc, 636 F.2d at 752. Once CVM has satisfied the initial burden, the burden shifts to the sponsor to establish the safety of the drug:

> In the Hess & Clark case we held that the "new evidence" requirement of the safety clause "plainly places on the [CVM] an initial burden to adduce the 'new evidence' and what that evidence 'shows'. Only when the [CVM] has met this initial burden of coming forward with the new evidence is there a burden on the manufacturer to show that the drug is safe." Rhone-Poulenc, 636 F.2d at 752 (quoting Hess & Clark, 495 F.2d at 992).

To meet its initial burden of proof to withdraw approval of a new animal drug that is "not shown to be safe," CVM must provide "a reasonable basis from which serious questions about the ultimate safety of [the drug] and the residues that may result from its use may be inferred." See Diethylstilbestrol: Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision (44 FR 54852 at 54861, September 21, 1979) (hereinafter DES Commissioner Decision) (quoting Proposal to Withdraw Approval of New Animal Drug Applications for Diethylstilbestrol, ALJ Initial Decision, Docket No. FDA-1976-N-0028 (formerly 76N-0002), I.D. at 8 (September 21, 1978)), aff'd Rhone-Poulenc, 636 F.2d 750; see also Nitrofurans Commissioner Decision (56 FR 41902 at 41902, August 23, 1991). Serious questions can be raised where the evidence is not conclusive but merely suggestive of an adverse effect. See DES Commissioner Decision.

C. Withdrawal Under the Delaney Clause and the DES Proviso

Section 512(e)(1)(B) of the FD&C Act provides grounds for withdrawal of approval of an NADA if new evidence, 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 may 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)-(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 edible tissues of or in any foods yielded from the animal (21 CFR part 500, subpart E). These regulations, referred to as the sensitivity of the method regulations (SOM regulations), describe how FDA determines whether the regulatory method proposed by a sponsor to detect no residues of the carcinogenic drug is sufficiently sensitive to ensure that residues of carcinogenic concern in edible tissues will not exceed concentrations that represent no significant increase in the risk of cancer to humans.

Pursuant to these regulations, CVM determines for each drug and each drug metabolite (on the basis of the results of chronic bioassays and other information) whether the drug or any of its metabolites should be regulated as a carcinogen (§ 500.84(a)). For the drug and each metabolite determined to be carcinogenic, CVM calculates, based upon 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 value 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). Residue of carcinogenic concern includes all compounds in the total residue of a demonstrated carcinogen excluding any compound judged by CVM not to present a carcinogenic risk (§ 500.82(b)). The total residues of carcinogenic concern (the drug and all of its metabolites less metabolites shown to be noncarcinogenic) are regulated based on the most potent carcinogenic residue (§ 500.84(c)(1)). 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 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 residues of carcinogenic concern in a specific edible tissue 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 test animals of 1 in 1 million. This value is termed the S_m (§§ 500.82(b) and 500.84(c)(1)).

Based upon residue depletion 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 (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)-(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, such that the absence of the marker residue in the target tissue above R_m can be taken as confirmation that the residue of carcinogenic concern does not exceed S_m in each of the edible tissues (§§ 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 diet of people 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 LOD [Limit of Detection for the regulatory method] must be less than or equal to R_m.")). 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. 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)).

As stated above, pursuant to section 512(e)(1)(B) of the FD&C Act, the Secretary shall, after due notice and an opportunity for a hearing, withdraw approval of an NADA if the Secretary finds that new evidence, 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 applies to the drug. Evidence that the Delaney Clause applies to a drug exists where the drug has previously been determined to be a carcinogen and the new evidence shows CVM's prior establishment of an analytical method and residue tolerance under the DES proviso exception to the Delaney Clause is inadequate. An analytical method is inadequate where new evidence demonstrates that the

method does not accurately detect the marker residue or where new evidence demonstrates that not all residues of carcinogenic concern have depleted at the approved tolerance level of the marker residue (see, e.g., Rhone-Poulenc, 636 F.2d at 752-53.)

In establishing that grounds for withdrawal of approval exist under this clause, CVM carries an initial burden to demonstrate that the new animal drug and/or any of its metabolites induces cancer when ingested by man or animals. Proposal to Withdraw New Animal Drug Applications for Furazolidone (NF-180) and Nitrofurazone (NF-7), ALJ Decision, FDA Docket No. FDA-1976-N-0511, at 73 (formerly 76N-0172; November 12, 1986) (hereinafter ALJ Decision, November 12, 1986). Once CVM has satisfied its initial burden, the sponsor bears the burden of showing that the drug satisfies the DES Proviso exception to the Delaney Clause and FDA's implementing regulations. ALJ Decision, November 12, 1986, at 73. ("Since furazolidone is also being challenged under the Delaney Clause, an additional issue…is whether new evidence put forth by the Center shows that furazolidone and/or its metabolites induces cancer when ingested by man or animal. If this burden is met, the sponsors must show [that the drug satisfies the DES proviso and FDA's implementing regulations]"); see also 21 CFR 500.92(b) (providing that for those compounds that FDA determines have been shown to induce cancer when ingested by man or animals, §§ 500.82 through 500.90 apply).

In this case, CVM had previously determined, in the approval and supplemental approvals of new animal drugs containing carbadox, that carbadox and its metabolites, including DCBX, induce cancer in animals, but that the drug could be approved under the DES Proviso exception to the Delaney Clause. See Section IV. However, new evidence raises questions about whether the drug is properly approved under the DES Proviso to the Delaney Clause and FDA's implementing regulations. See Criteria and Procedures for Evaluating Assays for

Carcinogenic Residues (44 FR 17070 at 17104, March 20, 1979) (reproposal of rules revoked in accordance with court order). ("[The FD&C Act] defines the new evidence that the Commissioner can consider in determining whether a previously approved compound is safe. [Proper analytical methods establishing residue levels] are necessary to show that a sponsored compound is safe under the FD&C Act. For that reason, the absence of data satisfying the [criteria in 512(e)(1)(B) of the FD&C Act], in conjunction with the evidence already available about a compound, clearly can support the withdrawal of approval of an application."). In particular, new evidence indicating that an approved regulatory method can no longer be relied upon is sufficient to satisfy the Agency's burden to support withdrawal of approval under section 512(e)(1)(B) of the FD&C Act and the Delaney Clause:

> In the case of an approved NADA for a carcinogenic compound, if FDA determines based on new information that the approved analytical method for detecting residues is inadequate…FDA could withdraw the approval on the basis of the Delaney Clause. Faced with evidence that an approved method was inadequate, FDA could not make a finding that "no residue" of the sponsored compound would be found in the edible products of treated animals. The DES Proviso cannot begin to operate without that finding, and, accordingly, the Delaney Clause would preclude continued approval. See Sponsored Compounds in Food Producing Animals; Criteria and Procedures for Evaluating Safety of Carcinogenic Residues; Proposed Rule (50 FR 45530 at 45550, October 31, 1985);[4] see DES Commissioners' Decision (44 FR 54852 at 54859, September 21, 1979).

In this case, new evidence raises serious questions both about the acceptability of the current method in determining levels of known carcinogenic residues of carbadox, and, further, demonstrates that previously unidentified carcinogenic metabolites exist that are entirely unaccounted for in current approved testing methodology. Because the current analytic method

[4]Under FDA's regulations implementing the Delaney Clause for animal drugs, part 500, subpart E, a carcinogenic drug may not be approved if the regulatory method to test for the compound is not sufficiently sensitive. §§ 500.84(c)(2) and 500.88(b). A carcinogenic drug will be withdrawn if new evidence shows that an approved regulatory method is not sufficiently sensitive.

is inadequate to identify the level of known carcinogens and does not identify the residue level of unidentified metabolites of carcinogenic concern, the current method and tolerance are inadequate to satisfy the DES Proviso.

D. Withdrawal Under the General Safety Clause

The General Safety Clause in section 512(e) of the FD&C Act provides grounds for withdrawal of approval of an NADA if new evidence, 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 drug is "not shown to be safe for use under the conditions of use upon the basis of which the application was approved" (section 512(e)(1)(B) of the FD&C Act). CVM has the initial burden to present new evidence that raises serious questions about the safety of the drug. Only upon that showing is there a burden on the manufacturer to demonstrate that the drug is safe. See Rhone-Poulenc, 636 F.2d at 752-53; Hess & Clark, 495 F.2d 975, 992 (D.C. Cir. 1974).

When evaluating a drug for withdrawal under the General Safety Clause, for CVM to satisfy its initial burden that new evidence raises serious human food safety questions, it must demonstrate a relationship between the drug residues found in edible tissues and risk to human health.

> [Without using] the Delaney Clause, it is not enough for the Commissioner merely to show that animal carcasses contain residues and that [the drug] is a carcinogen. Instead, the FDA must show that two different issues are resolved in its favor before it can shift to petitioners the burden of showing safety: (1) whether the detected residues are related to the use of [the drug]; (2) if so, whether the residues, because of their composition, and in the amounts present in the tissue, present some potential hazard to the public health. See Hess & Clark, 495 F.2d at 992 (D.C. Cir. 1974).

Applying this test, the D.C. Circuit Court of Appeals has held that new evidence of drug residues in edible tissues in conjunction with evidence that any drug residues of the drug in

question present safety concerns is sufficient to satisfy CVM's burden of raising serious questions regarding the safety of the drug. See Rhone-Poulenc, 636 F.2d at 752-53. CVM, acknowledging the Hess & Clark standard and its subsequent application, has withdrawn approval of a new animal drug under the General Safety Clause where new evidence showed that: (1) The new animal drug was carcinogenic; (2) some drug metabolites were mutagenic; and (3) residues left in edible tissues at the withdrawal time were unidentified. See Nitrofurans Commissioners' Decision, 56 FR 41902 at 41910, August 23, 1991 ("Since the nature of these residues and their toxicity were not evaluated, they cannot be regarded as safe... Contrary to the sponsors' assertions, the evidence fails to demonstrate that furazolidone's metabolites pose no health risk to the human consumers. Given all the other evidence in the record demonstrating that furazolidone is a carcinogen and that its metabolites are mutagens, I find that, contrary to the sponsors' assertions, the metabolites of furazolidone pose a potential health risk to human consumers.") see also DES Commissioners' Decision, 44 FR 54852 at 54868 (explaining that, "[w]here new evidence shows that use of the drug results in residues of unidentified substances," CVM must decide whether, despite this lack of knowledge, "the drug may be considered to be 'shown to be safe[,]' " as the General Safety Clause requires). In other words, because residues of a mutagenic carcinogen are presumptively carcinogenic, and therefore presumptively unsafe, where new evidence demonstrates that unidentified residues of a mutagenic carcinogen remain at the time of withdrawal, the drug meets the standard set forth in Hess & Clark.

Applying the Hess & Clark standard here, the new evidence regarding carbadox clearly meets both prongs of that test. New evidence demonstrates that previously unidentified mutagenic residues of carbadox, a known carcinogen, remain present well after the established withdrawal period. As discussed further in Section V.D., because carbadox is a mutagenic

carcinogen and QCA is the only known quantified noncarcinogenic residue of carbadox, all other residues are of carcinogenic concern. The new evidence demonstrates that the total residues of carcinogenic concern at the established 42-day withdrawal period are much higher than previously thought because the residues are no longer shown to be residues related to a noncarcinogenic compound, QCA, as previously believed. See, infra, Section V.D. Thus, the new evidence demonstrates that: (1) The unidentified residues are related to the use of carbadox and (2) the residues pose a potential hazard to public health because of the amount present and because they are residues of carcinogenic concern.

IV. Regulation of Residues of Carbadox

A. 1972 and 1975 Approvals

Carbadox is a carcinogen and was approved as a new animal drug pursuant to the DES Proviso exception to the Delaney Clause. At the time of the initial approval of carbadox in 1972, CVM (then the Bureau of Veterinary Medicine) recognized that carbadox is a carcinogen and therefore required that no residues of carbadox or its metabolite QCA be found in uncooked edible tissues of swine at the time of slaughter, as determined by the approved method of analysis. See 37 FR 20683, October 3, 1972, as amended by 37 FR 23906, November 10, 1972. This approval occurred prior to FDA's 1987 initial issue of regulations implementing the DES Proviso and therefore did not involve the development of a regulatory method sensitive enough to detect a marker residue that corresponded to a lifetime risk of cancer to test animals of 1 in 1 million (as described in Section III.C).

In this initial approval, based upon the submission of studies showing the depletion of carbadox residues in edible tissues, CVM determined that "[a]ll tissues except the liver [were] free of all residues" of unchanged carbadox at 24 hours after withdrawal of treatment and that

unchanged carbadox "ha[d] disappeared from the liver after 24 hours" (Ref. 8). CVM also determined from submitted studies that the carcinogenic parent drug was undetectable in liver at 24 hours (Id.). CVM further determined that a "restriction of use in the labeling provides a withdrawal period long enough [70 days] to assure no hazard to humans consuming residues in meat. In proper use there would be virtually no residues" of carbadox in tissues at slaughter (Ref. 9). The conclusions CVM made in 1972 regarding the rapid depletion of carcinogenic residues were later independently corroborated by a 1990 evaluation of carbadox by JECFA (Ref. 10 at p. 30).

Labeled use restrictions, as the drug was approved in 1972, included an upper weight limit of 75 pounds body weight and a prohibition on mixing into complete feeds containing less than 15 percent crude protein, thus limiting the drug's use to young pigs. These use restrictions provided assurances that the 70-day withdrawal period would likely be followed in practice (Ref. 11).

Similarly in 1975, FDA approved NADA 092-955 for the use of carbadox with pyrantel tartrate in Type C medicated swine feed (40 FR 45164, October 1, 1975). At that time, CVM reviewed drug residue studies of carbadox and pyrantel tartrate used in combination. The studies showed that, at 45 and 60 days withdrawal, concentrations of residues of carbadox in all tissues tested were undetectable using the previously approved analytical method with a 30 ppb limit of detection (Ref. 12 at p. 2).

B. 1986 Citizen Petition

On May 9, 1986, the Center for Science in the Public Interest submitted a citizen petition requesting that FDA withdraw approval of new animal drug applications for ipronidazole, dimetridazole, and carbadox (Ref. 13). The petition asserted that FDA must withdraw the

approval of carbadox because carbadox and its metabolites DCBX and hydrazine were found to be carcinogenic, and the approved test method for carbadox residues is "unsuitable" (Ref. 13 at p. 20). The asserted unsuitability of the approved test method was based upon the fact that only a small portion of total residues had been positively identified and that the analytical method for carbadox residues was not sensitive enough to ensure that all residues had depleted.

FDA responded to the 1986 citizen petition in 1995 after a review of new residue depletion data submitted by (the then sponsor) Pfizer as well as data previously submitted to the Agency as part of the carbadox NADAs. Based upon this review, FDA denied the petition as it related to carbadox because it determined that "if used according to label directions, residues of carbadox remaining in edible tissues of swine do not pose a human food safety risk to consumers" (Ref. 14 at p. 2). FDA based this safety determination on the following findings:

> 1. At 70 days withdrawal, the drug-related residue in swine liver measured 13 ppb. 2. Ten percent of the drug-related residue was extractable and identified to be a noncarcinogenic metabolite, quinoxaline-2-carboxylic acid. 3. The remaining 90% of the drug-related residue was unextractable or bound residues. 4. The bound residues were related to quinoxaline-2-carbodoxaldehyde and quinoxaline-2-carboxylic acid, both of which are of no carcinogenic concern. (Ref. 14 at p. 1).

C. Approval of 1998 Supplemental NADAs

In 1998, FDA approved two supplemental applications to NADA 041-061. The first supplement, approved in January 1998, assigned the noncarcinogenic metabolite QCA as the marker residue and set a tolerance of 30 ppb QCA in swine liver (Ref. 1).

Toxicology studies, including carcinogenicity bioassays with carbadox, DCBX (a primary metabolite of carbadox), and hydrazine were submitted as part of that supplemental application (Ref. 1 at pp. 1-5). The studies demonstrated the carcinogenicity of carbadox, DCBX, and hydrazine, and indicated that DCBX was the most potent of the three carcinogenic compounds (id.). Consequently, based on DCBX, CVM calculated an S_o of 0.061 ppb for total

residues of carcinogenic concern for carbadox in the total diet (Ref. 1 at p. 5). CVM calculated an S_m value for total residues of carcinogenic concern in muscle at 0.305 ppb, in liver at 0.915 ppb, and in kidney and fat at 1.830 ppb (Ref. 1 at pp. 8-9).

The SOM regulations, as they existed in 1998, directed CVM to establish an R_m for carcinogenic compounds used in food-producing animals. CVM did not establish an R_m because CVM concluded the parent carbadox was rapidly metabolized, carcinogenic residues were not detectable beyond 72 hours post dosing, and unextracted residues[5] were related to noncarcinogenic QCA and not of carcinogenic concern. Because the noncarcinogen QCA was the only detectable metabolite persisting beyond 72 hours post dosing, CVM assigned it as the marker residue (id.).

At the time it approved the supplement in January 1998, CVM said:

> The sponsor and academic researchers have conducted numerous studies evaluating the fate of carbadox in animals. These residue depletion data are summarized in FAO Food and Nutrition Paper 41/3 (Food and Agriculture Organization (FAO) of the United Nations, 1991) and 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 <u>in vivo</u> metabolism of the compounds of carcinogenic

[5]Unextracted residues are residues of the drug that are not released when tissues are exposed to mild aqueous or organic extraction conditions. Guidance on analysis of unextracted total radiolabeled residue is provided in "Guidance for Industry: General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals (GFI #3)," 2006. Unextracted or bound residues can be either: (1) Endogenous components resulting from fragments of the radiolabeled compound being incorporated into naturally occurring molecules such as amino or nucleic acids or (2) covalently bound residues. Covalently bound residues are considered to be of toxicological concern and their availability for absorption into the human gastrointestinal tract is considered during an evaluation of human food safety. Residues incorporated into endogenous molecules are not considered bioavailable or to be of toxicological concern. However, CVM has determined that establishing a potentially carcinogenic compound is bound and not of carcinogenic concern can be complicated by the possibility of gastrointestinal binding and gastrointestinal carcinogenesis and consequently can involve a more comprehensive assessment of the bound compounds as described in GFI #3. Note that while CVM has recognized that carbadox residues have not been fully extracted and characterized, CVM has not made an assessment that the compounds are not carcinogenic because they are bound to endogenous molecules (Ref. 15 at pp. 3-4). Moreover, residue studies presented to JECFA in 2003 suggest that carcinogenic residues that had not been extracted when exposed to organic extraction were released by simulated digestive enzymes (Ref. 2 at pp. 7-8, Table 5).

> 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 quinoxaline-2-carboxylic acid [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. (Ref. 1 at p. 9).

CVM established a tolerance of 30 ppb for residues of QCA in liver, the tissue in which residues persist for the longest time. CVM concluded that the concentration of residues of carcinogenic concern in edible tissues was below the S_m when the concentration of QCA in liver had depleted to 30 ppb.[6]

> Under FDA's operational definition of "no residue," a residue of carcinogenic concern, so long as it does not exceed the S_o, may be detectable by an approved method. The residue data show that carbadox, desoxycarbadox and hydrazine do not persist in edible tissue as detectable residues beyond 72 hours. The in vivo metabolism of the compounds of carcinogenic concern is irreversible. Therefore, in this case, no residue of carcinogenic concern, even below the S_o, is detectable by any method. The unextracted residues are related to a noncarcinogenic compound, quinoxaline-2-carboxylic acid (QCA), and extractable QCA is the only residue detectable in the edible tissues 72 hours postdosing. Thus, the agency concludes that QCA is a reliable marker residue for carbadox and its metabolites.
>
> From these data, FDA has selected liver as the target tissue and quinoxaline-2-carboxylic acid (QCA) as the marker residue. FDA has determined that when QCA, the marker, is at or below 30 ppb in the target tissue, liver, that no residue of carcinogenic concern, above the S_o, is detectable in each of the edible tissues by any method.
>
> The sponsor has submitted a regulatory method capable of measuring QCA at and below 30 ppb in the target tissue. (Ref. 1 at p. 14).

As part of their application supporting the January 1998 supplemental approval, the sponsor submitted a regulatory method for residues of QCA in swine liver. The regulatory method relies on a gas chromatograph assay with electron capture detection and has a limit of

[6]The SOM regulations, as they existed in 1998, permitted approval of a regulatory 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. See § 500.86(c) (1998).

quantification of 5 ppb (Ref. 1 at p. 13), a 6-fold improvement of the sensitivity from the previously approved regulatory method (Ref 1.)

In October 1998, FDA approved an additional supplement to NADA 041-061 changing the withdrawal period for carbadox medicated feeds from 70 days to 42 days. The supplement was approved based upon the previous approval of a tolerance of 30 ppb for QCA and a residue depletion study that showed that residues of QCA in liver depleted below 30 ppb by 42 days (Ref. 16).

To summarize, in 1998, when FDA approved supplements to NADA 041-061 establishing a drug tolerance and shortening the withdrawal period, the evidence before CVM indicated:

- A 0.915 ppb concentration of total residues of carcinogenic concern in liver is the concentration that represents no significant increase in the risk of cancer to people--total residues of carcinogenic concern in liver above 0.915 ppb under the drug's approved conditions of use are unsafe. Such residues would preclude continued approval because the drug would not be shown to be safe and because the exception to the Delaney Clause would not apply (Ref. 1 at pp. 8-9, 10, 14).
- The parent compound carbadox is rapidly metabolized and carcinogenic residues of the drug are not identifiable in any edible tissues beyond 72 hours post dosing (Ref. 1 at p. 9).
- Remaining unextracted residues of carbadox are noncarcinogenic residues related to the noncarcinogenic metabolite QCA (Ref. 1 at pp. 9, 14).
- QCA is a reliable marker residue for carbadox and its metabolites; that is, measuring QCA residues in swine liver is a valid method for demonstrating the absence of residues of carcinogenic concern in edible tissues (id.).

Based upon these conclusions, CVM found that under the conditions of use the drug did not result in unsafe residues of carcinogenic concern in edible tissues and that the use of carbadox, as approved in the NADA supplements, satisfied the DES Proviso exception to the Delaney Clause prohibition on carcinogenic animal drugs (id.).

D. Approval of the 2004 Feed Use Combination

In 2004, FDA approved a combination drug medicated feed containing carbadox and oxytetracycline under NADA 141-211 (Ref. 17). In accordance with section 512(d)(4)(A) of the FD&C Act, approval of a combination new animal drug, where the underlying new animal drugs have previously been separately approved for particular uses and conditions of use for which they are intended for use in the combination, will not be refused on human food safety grounds unless the application fails to establish that: (1) None of the animal drugs used in combination, at the longest withdrawal period for any of the drugs in the combination, exceeds its established tolerance or (2) none of the drugs in the combination interferes with the method of analysis for any of the other drugs in the combination (section 512(d)(4)(A)(i)-(ii) of the FD&C Act). In other words, in order to approve a combination new animal drug for a drug product that contains two previously approved new animal drugs, no new information needs to be supplied to establish the safety of either drug. Instead, the application need only demonstrate that use of the drugs in combination will not result in violative residues of any component drug or in drug assay interference.

Both carbadox and oxytetracycline had been previously and separately approved by FDA for the same conditions of use proposed for their use in combination. See 21 CFR 558.450 (Oxytetracycline); § 558.115 (Carbadox). The sponsor, Phibro, provided tissue residue depletion data demonstrating that QCA residues did not exceed the tolerance of 30 ppb when carbadox was

administered in conjunction with oxytetracycline to swine (Ref. 17). A pharmacokinetic study comparing blood levels of oxytetracycline when administered alone and when administered in conjunction with carbadox satisfied the need to demonstrate that residues of oxytetracycline would not exceed the oxytetracycline tolerance at 42 days (id.).

The sponsor further provided data demonstrating noninterference of oxytetracycline with the method of analysis of QCA in liver (id.). Having made the required human food safety demonstrations for combination animal drugs, there was no basis to refuse approval of the product on human food safety grounds. The combination new animal drug was subsequently approved (id.).

V. New Information Regarding Carcinogenic Residues in Edible Tissues

Three sources provide new information regarding carcinogenic residues in edible tissues: Data submitted to the 2003 JECFA and the subsequent JECFA report (Ref. 2) and two publications in the peer-reviewed literature (Refs. 4 and 6).

JECFA is an internationally recognized expert body, providing the scientific evaluations that become the basis for international food standards established by the Codex Alimentarius Commission and supporting international treaties such as the Sanitary Phytosanitary Agreement. JECFA experts are chosen based on expertise, reputation, assurance of lack of conflict of interest, and familiarity with the subject of that particular evaluation.

In addition, pursuant to section 512(l)(1) of the FD&C Act[7], FDA ordered Phibro to provide it with the same data provided to the 2003 JECFA. CVM evaluated the submitted data and found that it raised questions regarding the safety of food resulting from swine treated with

[7]An order issued pursuant to section 512(l) of the FD&C Act, requires a sponsor to submit such data and information as FDA may find necessary to determine or facilitate a determination whether grounds to withdraw approval of an NADA under section 512(e) of the FD&C Act exist.

carbadox. Confidence in the information evaluated by the 2003 JECFA that is the basis for CVM's concern about carbadox was increased by the independent findings reported in the two publications discussed further.

A. New Information Provided to JECFA

In 2003, at the request of the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), JECFA reevaluated the recommended Maximum Residue Limits (MRLs) for carbadox that were based upon a 1990 JECFA evaluation of the new animal drug (Ref. 2). CCRVDF, which includes CVM as a participant, determines priorities for the consideration of residues of veterinary drugs in foods and recommends MRLs for veterinary drugs to the Codex Alimentarius Commission of the Food and Agriculture Organization and the World Health Organization of the United Nations. The Codex Alimentarius Commission develops harmonized international food standards, guidelines, and codes of practice to protect the health of the consumers and ensure fair practices in food trade (see footnote 2).

Based on studies submitted to JECFA that 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. JECFA recommended that the Codex MRLs be withdrawn. CCRVDF concurred with JECFA's recommendation and proposed to the Commission that the MRLs be withdrawn. The Commission subsequently agreed and withdrew the Codex MRLs for carbadox (Ref. 18 at p. 120).

As part of the JECFA reevaluation process, Phibro presented two new residue studies to JECFA in 2003. Only one of these studies involved measurement of the depletion of carcinogenic metabolites of carbadox in edible tissues. In that study, animals were fed for 14 days at the approved dose of 55 ppm carbadox in feed (Ref. 2 at pp. 6-10). Animals were

euthanized at various time points between 0 hours and 15 days post treatment, and samples of swine muscle, liver, skin, and fat were collected (Ref. 2 at pp. 7-8, Table 5).

Prior to analysis for residues, some of the tissue samples were exposed to human digestive enzymes[8] (Ref. 2 at p. 7). This in vitro model of bioavailability was designed to mimic effects of gastric fluid and intestinal fluid incubation in human stomach and small intestine to evaluate whether residues potentially could be released in the human gastrointestinal tract. To allow comparison, some tissue samples were left untreated while other tissue samples were incubated in simulated gastric fluid (with pepsin) or in simulated intestinal fluid (with pancreatin). Residues of carbadox, DCBX, and QCA were measured in the untreated tissues, in tissues that were incubated with enzymes, and in the supernatant of those tissues that were incubated with enzymes (id.).

Residues of carbadox, DCBX, and QCA were measured by liquid chromatography-atmospheric pressure chemical ionization tandem mass spectrometry (LC/APCI-MS/MS). The tissue samples that were not incubated with enzymes were extracted with acetonitrile prior to analysis. The tissue samples that were incubated with enzymes were extracted with ethyl acetate prior to analysis. Supernatants of the enzyme digestion were analyzed directly without extraction. The limits of quantification for LC/APCI-MS/MS were 0.050 ppb for carbadox residues and 0.030 ppb for DCBX residues (id.). The detection capabilities of this methodology were greatly enhanced compared to the previous method for carbadox and DCBX (i.e., the method used for the previous analytical work had a detection limit of 2 ppb) (Ref. 20).

[8]The use of enzymic preparations to characterize residues is described in section 2.3.4.3.2 of CVM Guidance for Industry (GFI) #205 VICH GL 46, "Studies to Evaluate the Metabolism and Residue Kinetics of Veterinary Drugs in Food-Producing Animals: Metabolism Study to Determine the Quantity and Identify the Nature of Residues (MRK)," Sept. 15, 2011 (Ref. 19).

The study presented to JECFA showed that residue concentrations of carbadox and DCBX were higher and persisted for a longer period post dosing in liver than in the other sampled tissues. In liver without treatment with simulated digestive fluids, carbadox was detectable (0.050 ppb) as long as 48 hours post dosing and DCBX was detectable (0.138 ppb) at the last sampling time point, which was 15 days post treatment (Ref. 2 at pp. 7-8, Table 5). Treatment of tissues with simulated digestive fluids resulted in measurement of significantly higher concentrations of DCBX. "Pretreatment of the samples with digestive fluids increased the amounts of carcinogenic residues found in all tissues. In liver the concentration of …[DCBX] increased by more than fourfold when the samples were treated with intestinal fluid, and large quantities were present 15 days after withdrawal…" (Ref. 2 at p. 17).

In particular, the study showed that concentrations of approximately 35 ppb of DCBX at 0 hours post dosing and approximately 2.7 ppb of DCBX at 15 days post dosing were measured in liver treated with pancreatin (Ref. 2 at p. 8, Table 5). The significantly increased residues found in liver after treatment with intestinal enzymes show that enzymatic treatment was able to release carcinogenic residues that were not extractable by organic solvents, such as those used in tissue residue studies to support the original and supplemental approval of NADAs for use of carbadox.

JECFA evaluated the percent recoveries of the analytes. Percent recovery is a measurement of accuracy of the analytical procedure and expresses the closeness of agreement between the true value of the analyte concentration and the mean value obtained by applying the analytical procedure (Ref. 21). JECFA reported that when carbadox, DCBX, and QCA were incubated for 4 hours with digestive enzymes, carbadox and DCBX were unstable (percent recovery decreased) in the samples treated with pepsin, but were stable in pancreatin (Ref. 2 at p.

16). JECFA also reported that the recoveries of the analytes from the liver samples were generally variable and decreased to low levels when digestive enzymes were used prior to extraction (Ref. 2 at pp. 17-18).

After evaluating the residue study, JECFA concluded that the poor recoveries obtained with the enzyme experiments "showed that the true concentrations of the carcinogenic metabolites in tissues cannot yet be estimated with certainty, since an unknown portion of the releasable residue [of carbadox and DCBX] is destroyed during incubation [of liver tissues] with the [digestive] enzymes" (Ref. 2 at p. 18). JECFA therefore concluded that the measured values of DCBX and carbadox "represent[ed] a lower estimate of the total present in the tissue" (id.).

Presented with data demonstrating both the depletion of QCA and depletion of the carcinogenic residue DCBX, JECFA established a relationship between the concentrations of QCA and DCBX in liver (Ref. 2 at p. 14). The statistical analysis of the data showed a linear relationship between the logarithms of the concentrations of QCA and DCBX (Ref. 2 at pp. 14, 18). This relationship allowed JECFA to use regression analysis to assess the concentrations of DCBX when QCA depleted to 30 ppb in liver (the Codex MRL and FDA approved tolerance for carbadox). JECFA determined that "[a]t the MRL [of 30 ppb] for QCA in liver, the average concentrations of the carcinogenic residue desoxy-carbadox in liver estimated by regression analysis were about 4 [ppb]" (Ref. 2 at pp. 14, 16-17). JECFA recognized that "tolerance limits for the concentration of desoxycarbadox were several times higher owing to the wide variation of the data" and thereby concluded that "QCA is not a suitable marker for monitoring carcinogenic metabolites of carbadox in liver…and QCA does not ensure the absence of carcinogenic residues" (Ref. 2 at p. 17).

In contrast to the previous findings of JECFA, these new data show that carcinogenic residues, in particular DCBX, are present in edible tissues for a significant time during the depletion of parent carbadox (Ref. 2 at p. 18). Moreover, the study shows that treatment with simulated digestive enzymes releases higher levels of the carcinogenic residues DCBX than were recovered using organic extractions in the study. These higher concentrations provide evidence that the carbadox residues that were not extractable or identified in previous studies submitted to the Agency could include carcinogenic residues of carbadox that are releasable with enzymatic treatment of tissues. This evidence calls into question the Agency's previous conclusions that all unextracted and unidentified residues were noncarcinogenic residues related to QCA.

After reviewing the new residue data, and considering the previously evaluated genotoxicity and carcinogenicity data, JECFA recommended withdrawal of the previously established Codex MRLs (Ref. 2 at p. 18). Codex subsequently agreed and withdrew the MRLs for carbadox (Ref. 18 at p. 120).

In summary, the studies considered by JECFA during its 2003 review of the drug indicated that:

- Residues of the carcinogenic metabolite of carbadox, DCBX, were measured in edible tissues for 15 days, which was the last sampling time point. DCBX was measured in swine liver after treatment with simulated digestive enzymes at concentrations as high as 2.69 ppb at 15 days post treatment (Ref. 2 at p. 8, Table 5).
- Analysis of measured concentrations of QCA and DCBX in liver indicated that approximately 4 ppb of DCBX would be present in the liver of treated animals when QCA reached the Codex MRL and the FDA tolerance of 30 ppb in liver (Ref. 2 at pp. 14, 17). This concentration of DCBX alone is more than 4 times higher than the

concentration of total residues of carcinogenic concern in liver that would present no significant increase in the risk of cancer to people.

- Residues of carbadox previously unextracted from edible tissues could be released by gastric and intestinal fluids that mimic the human digestive process (Ref. 2 at p. 16). The enzymatic treatment used in the study significantly increased the recoveries of concentrations of DCBX and carbadox from edible tissues, thereby indicating that some portion of the previously unextracted and unidentified total residues is composed of carcinogenic compounds.

B. Additional New Evidence

Following the reports of the 2003 JECFA reevaluation of carbadox, CVM requested that Phibro also provide the carcinogenic residue depletion study to CVM. In 2005, in response to CVM's request for information, Phibro submitted a summary of the carcinogenic residue depletion study previously provided to JECFA. Upon review of the summary data, CVM asked Phibro to submit existing studies or provide new and complete studies that address the relationship of QCA at 30 ppb and carbadox and DCBX residues, and about the use of QCA as the marker residue for surveillance purposes. In 2006, CVM asked for and received from Phibro a timeline for submission of complete information that addresses concerns about the relationship of QCA at 30 ppb and carbadox and DCBX residues, and about the use of QCA as the marker residue for surveillance purposes. Between 2006 and 2011, interactions between CVM and Phibro continued, with protocols submitted and reviewed, method validation reports submitted and reviewed, informal communications by email, and informal discussions by telephone. The focus of the interactions was development and validation of methods to measure QCA and

DCBX in a tissue residue depletion study. Despite the continued interaction between Phibro and CVM, Phibro has not submitted the requested information.

In 2011, pursuant to section 512(l)(1) of the FD&C Act, FDA ordered Phibro to provide all information in its possession with respect to: (1) The persistence of DCBX in edible tissues; (2) the appropriateness of QCA as an analyte for residue monitoring and for establishing a withdrawal time for the use of carbadox in pigs; and (3) whether an analytical method for monitoring carbadox-related carcinogenic residues in edible tissues can be developed that would comply with part 500, subpart E.

In response to the 2011 FDA order, Phibro provided CVM with the full study report and appendices, previously provided to JECFA in 2003.

CVM has independently evaluated the data from the Phibro study of depletion of carcinogenic residues reviewed by JECFA in 2003, and in particular has reviewed the JECFA conclusion that when QCA reaches 30 ppb in liver, residues of DCBX in liver are "estimated by regression analysis to be about 4 [ppb]" (Ref. 2 at p. 18). CVM's statistical analysis of the residue concentrations of DCBX in liver treated with pancreatin (a simulated intestinal fluid) shows that concentrations of DCBX in liver, when QCA reaches the 30 ppb approved tolerance, would average 4 ppb and, based on the data in the JECFA report, could reasonably range from 1.4 ppb to 11 ppb, using a 95 percent prediction range. Based upon this analysis, DCBX alone--leaving aside additional, unidentified residues of carcinogenic concern--significantly exceeds the approved S_m when QCA, the approved marker residue, reaches the approved tolerance. The new evidence from the 2003 JECFA re-evaluation of carbadox, along with studies that were later submitted to CVM, undermine the human food safety conclusions that CVM had previously reached when considering the approval of the new animal drug applications for carbadox for its

various uses. CVM has engaged with Phibro to evaluate the carbadox-associated safety concerns raised by the new evidence and repeatedly has asked Phibro to submit information that would address these safety concerns. Information provided by Phibro in response to these requests has not resolved CVM's human food safety concerns.

1. Boison, et al., 2009

In addition, a 2009 publication calls into question conclusions made by CVM when it approved the NADAs and supplemental NADAs for carbadox (Ref. 4). Boison, et al., 2009, demonstrates the availability of a sensitive analytical method for DCBX, and provides information from which serious questions about the safety of carbadox can be inferred, specifically whether DCBX may be present in edible tissues of treated swine above the S_m even when the marker residue (QCA) concentration is below the tolerance of 30 ppb (id.).

Boison, et al., report: (1) QCA is not a suitable marker for the regulation of carbadox because while QCA is very stable under temperature conditions above 60 °C (i.e., 105 °C), DCBX is not (Ref. 4 at p. 133); (2) the existence of an analytical method capable of detecting DCBX below the S_m for porcine muscle and liver (Ref. 4 at p. 132, Table 5); and (3) detection of DCBX at a concentration greater than 0.050 ppb in the diaphragm (but not the liver) of 2 of 6 hogs fed carbadox, while QCA was not detected in the liver of those same hogs at a limit of quantitation (LOQ) of 0.500 ppb (Ref. 4 at pp. 132-33). The findings of Boison, et al., are significant for two reasons: (1) QCA appears not to be a reliable marker residue and (2) DCBX is reported to be sensitive to the processing temperature used in the analytical method.

2. Baars, et al., 1991

In 2012, in response to FDA's 2011 order under section 512(l) of the FD&C Act, Phibro sent CVM a letter citing Baars, et al., 1990 (Ref. 5), an abstract of a study not previously

provided. CVM obtained the study report Baars, et al., 1991 (Ref. 6), which reports an analytical method with a limit of detection of 1 ppb that detects the presence of DCBX in edible tissues for greater than 72 hours after removal of feed containing carbadox. Specifically, Baars, et al., 1991, demonstrated the presence of DCBX for up to 7 days (~168 hours) in the kidney and 14 days (~336 hours) in the liver of swine fed carbadox (Ref. 5 at p. 3, Fig. 3; Ref. 6 at p. 290, Fig. 2). This observation called into question CVM's previous conclusion that all residues of carcinogenic concern deplete within 72 hours.

C. New Evidence Calls into Question Prior CVM Conclusions That Were the Basis of the 1998 Supplemental Approval

CVM's prior conclusion that QCA is a reliable marker residue for carbadox and its metabolites was predicated on several underlying conclusions (Ref. 1 at pp. 13-14). These underlying conclusions are reviewed below in light of the new evidence presented above.

1. Previous Conclusion 1: The residue data show that carbadox, DCBX, and hydrazine do not persist in edible tissues as detectable residues beyond 72 hours.[9]

Since the time CVM made this previous conclusion, we have become aware of information that undermines the previous conclusion that carbadox and its carcinogenic metabolites do not persist in edible tissues beyond 72 hours. JECFA, in 2003, reviewed a study detecting DCBX in livers of swine up to 15 days after cessation of carbadox exposure. The study JECFA reviewed was limited to 15 days. The data presented to JECFA in 2003 provide new scientific evidence that DCBX persists in edible tissues of swine as a detectable residue beyond 72 hours (Ref. 2).

[9]This underlying conclusion is described in the January 30, 1998, summary basis of approval under the Freedom of Information Act (FOI Summary) for NADA 041-061 (Ref. 1 at p. 9) and in the report of the 1990 JECFA meeting (Ref. 10 at p. 30).

Further, Baars, et al., 1991, reports detecting DCBX in liver up to Day 14 after cessation of exposure to carbadox using an analytical method with a detection limit of 1 ppb (Ref. 6). Baars, et al., 1991, provides new scientific evidence that DCBX persists as a detectable residue in edible tissues of swine for greater than 72 hours.

Scientific evidence from JECFA's 2003 evaluation of submitted information and Baars, et al., 1991, demonstrate that DCBX, one residue of carcinogenic concern for carbadox, persists in edible tissues of swine beyond 72 hours. All of this evidence was first received by CVM after the 1998 approval of the supplemental application to NADA 041-061. Based on this new scientific evidence, the previous conclusion that DCBX does not persist in edible tissues of swine as a detectable residue beyond 72 hours is no longer justified.

2. Previous Conclusion 2: The unextracted residues are related to a noncarcinogenic compound, QCA, and extractable QCA is the only residue detectable in the edible tissues of swine 72 hours post dosing.[10]

At the time of the 1998 supplemental approval, CVM concluded that that unextracted residues were related to the noncarcinogenic compound, QCA, and that extractable QCA was the only residue detectable in the edible tissues after 72 hours post dosing. However, CVM is now aware of reports of extraction of residues being enhanced by pepsin or pancreatin digestion prior to organic extraction, making non-QCA residues previously thought to be unextractable currently extractable (Ref. 2). JECFA reports that some residues of carbadox previously identified as unextractable can now be extracted (id.). DCBX was found in the newly extractable residues.

[10]This underlying conclusion is described in the January 30, 1998, summary basis of approval under the Freedom of Information Act (FOI Summary) for NADA 041-061 (Ref. 1 at p. 9) and in the report of the 1990 JECFA meeting (Ref. 10 at p. 30).

This scientific evidence demonstrates that some residues previously found to be unextractable are extractable and that the unextractable residues are not all related to QCA.

As discussed above, residues of DCBX, a residue of carcinogenic concern, have been detected in edible tissues longer than 72 hours post dosing (Refs. 2, 5, and 6). The previous underlying conclusions that unextracted residues are related to noncarcinogenic compound, QCA, and extractable QCA is the only residue detectable in the edible tissues 72 hours post dosing is no longer justified based on new scientific evidence.

3. Previous Conclusion 3: No residue of carcinogenic concern even below the S_0, is detectable by any method beyond 72 hours.[11]

Boison, et al., 2009, reports a method capable of detecting DCBX at 0.05 ppb, which is below the 0.061 ppb S_o and below the S_m of 0.305 ppb in muscle, 0.915 ppb in liver, and 1.83 ppb in kidney and fat. The method is also capable of measuring QCA at 0.500 ppb, below the current tolerance of 30 ppb (Ref. 4 at p. 132, Table 5). Consequently, measurement of the relationship of QCA to at least one residue of carcinogenic concern, DCBX, is now scientifically feasible at the time the last tissue depletes to its S_m. In fact, Boison, et al., 2009, reports the presence of DCBX at a concentration greater than 0.050 ppb in the diaphragm (muscle) of 2 of 6 market-weight hogs fed carbadox, when QCA was not detected, at a limit of quantitation of 0.50 ppb, in the livers of those same hogs (Ref. 4 at pp. 132-133). This evidence raises a serious question about whether QCA at 30 ppb is an appropriate marker residue for carbadox residues of carcinogenic concern. Based on this new scientific evidence, the previous underlying conclusion that no residue of carcinogenic concern, even below the S_O, is detectable by any method beyond 72 hours is no longer justified.

[11]This underlying conclusion is part of the basis of the January 1998 supplemental approval (FOI Summary)(Ref. 1 at pp. 13-14).

4. Previous Conclusion 4: QCA is a reliable marker residue for carbadox and its metabolites.[12]

In light of the new evidence presented above, the conclusion that QCA is a reliable marker residue for carbadox and its metabolites is no longer justified because: (1) Previous conclusions made by the Agency are no longer scientifically justified and (2) the relationship of QCA to a carbadox residue of carcinogenic concern, DCBX, in the last tissue to deplete to its S_m is not known.

D. CVM's Reanalysis of the Human Health Risk From Previously Submitted Residue Data

CVM reevaluated the existing carbadox residue data as a result of discussions that took place during meetings in 2011 with Phibro about the composition of total residues of carbadox (Refs. 3 and 22). CVM also reexamined the residue data submitted in support of the 1998 NADA supplements in light of the new understanding from the 2003 JECFA report that carcinogenic residues of carbadox persisted in edible tissues for 15 days, which was the last sampling time point, and that the previously unextractable residues are not necessarily noncarcinogenic residues related to QCA (Ref. 2).

Using data in the FOI Summary for the January 30, 1998, supplemental approval, CVM reviewed information on total residue concentrations (measured from total radioactivity present in tissue from swine administered the radiolabeled drug), as well as the percent of total residues represented by QCA--the only noncarcinogenic metabolite of carbadox identified and quantified in the total residues of carbadox (Ref. 1). CVM used the total residue data and the percent of total residues represented by QCA to calculate the total residue of carcinogenic concern present in liver. Under the SOM regulations, "residues of carcinogenic concern" in edible tissues are total residues of a carcinogenic drug minus identified residues that are judged by CVM to be

[12]This underlying conclusion is part of the basis of the January 1998 supplemental approval (FOI Summary)(Ref. 1 at pp. 13-14).

noncarcinogenic (§ 500.82(b)). CVM previously excluded the unextracted portions of total residues from carcinogenic concern because it believed they were noncarcinogenic, QCA-related residues. The data presented to JECFA in 2003 now refute that conclusion, and CVM has no information, from Phibro or otherwise, that identifies or measures noncarcinogenic residues other than QCA in total residues of carbadox at the withdrawal period. As such, CVM now identifies the total residue of carcinogenic concern by subtracting QCA (identified residues that are confirmed to be noncarcinogenic) from total residues of carbadox. Determining the concentration of residues of carcinogenic concern present in the liver allowed CVM to compare that value with the S_m established for residues of carcinogenic concern in liver.

CVM reviewed data regarding concentrations of total residues in swine tissues following 5 days of feeding ^{14}C-carbadox contained in a residue depletion study (the same study submitted to JECFA for its 1990 evaluation of carbadox (Ref. 10 at p. 31)) submitted by the sponsor in support of the supplemental application to NADA 041-061 approved in January 1998 (Ref. 1, Study No. 1525N-60-87-005). The study measured concentrations of total residues of ^{14}C-carbadox and residues of QCA. Using these data, the study reported QCA as a mean percentage of the total residues of carbadox. QCA represented 24.4 percent of the total residues at 30 days, 27.5 percent at 45 days, and 9.9 percent at 70 days post dosing (Ref. 1 at p. 13, Table 9).

Table 1 presents total carbadox residues and total carbadox residues minus the noncarcinogenic QCA. Column 1 lists the sampling time point when swine were slaughtered following administration of the last dose of carbadox. Column 2 presents mean total residues measured in livers collected from swine slaughtered at each time point. Column 3 lists the mean QCA percentage of total residues at each time point. Column 4 lists the calculated mean total

residues of carcinogenic concern based on a subtraction of QCA from the mean total residue values in Column 2.

Table 1.--Mean Total Residues Measured as ^{14}C-carbadox Equivalents, the Mean Percentage of Total Residues Represented by QCA, and Mean Total Residue of Carcinogenic Concern in Liver of Swine (n=3 or 4) Following 5 Days of Feeding ^{14}C-carbadox at 55 ppm

Days Post Dosing	Total Residues (ppb)	Percent QCA	Total Residue of Carcinogenic Concern (ppb)[1]
30	74.5	24.4	56.3
45	20.0	27.5	14.5
70	13.3	9.9	11.98

[1] Values calculated by subtracting noncarcinogenic QCA portion from total residues.

FDA first approved the use of carbadox in 1972 prior to the issuance of the Agency's SOM regulations. CVM did not make a calculation comparing total residues less QCA to the S_m in approving the January 1998 NADA supplement because the data available at the time indicated that DCBX was not detectable beyond 72 hours post dosing (by the analytical method used at the time) and because CVM believed all unextractable residues were noncarcinogenic residues related to QCA (Ref. 1). No residue depletion data presented to the Agency in original or supplemental NADAs showed that carcinogenic residues persisted beyond 72 hours or that the unextractable residues were carcinogenic. As a result, CVM did not, at that time, ask for data regarding the composition of total residues beyond establishing QCA as an appropriate marker residue. New evidence presented to JECFA in 2003 and reported by Boison, et al., 2009, and Baars, et al., 1991, calls CVM's prior conclusions into question and places new significance on the concentrations of total residues of carcinogenic concern for carbadox (Refs. 2, 4, and 6).

The individual data shown as mean values in Table 1 were used to predict total residues of carcinogenic concern at the approved 42-day withdrawal period for carbadox in NADAs 041-061 and 141-211, and the approved 70-day withdrawal period for carbadox in NADA 092-955. CVM analyzed the data using the logarithm of the dependent variable (carbadox-equivalents in liver). The logarithmic transformation or "exponential model" is consistent with the published JECFA analyses of carbadox and commonly observed elimination behavior of pharmaceuticals

(Ref. 22). Using this modeling procedure, the total residues of carcinogenic concern at 42 days are estimated to be 27 ppb with a 95 percent prediction interval of 9 ppb to 80 ppb (Ref. 3 at p. 17, Table 8). These predictions can be compared with the S_m for swine liver of 0.915 ppb. The regression model predicts that swine liver concentrations of total carcinogenic residues will be significantly in excess of the S_m--approximately 30-fold (27 ppb ÷ 0.915 ppb = 29.51) greater residues of carcinogenic concern than the S_m at the approved 42-day withdrawal period for NADAs 041-061 and 141-211 (Ref. 3 at p. 16). Total residues of carcinogenic concern at 70 days are estimated to be 10 ppb with a 95 percent prediction interval of 3 ppb to 32 ppb (Ref. 3 at p. 17, Table 8). The analysis predicts that swine liver concentrations of total carcinogenic residues will be significantly in excess of the S_m--approximately 11-fold greater residues of carcinogenic concern than the S_m at the approved 70-day withdrawal period for NADA 092-955.

Approval of a carcinogenic new animal drug under the DES Proviso to the Delaney Clause requires development of a sufficiently sensitive regulatory method that detects no residues of carcinogenic concern in the edible tissues of food-producing animals from the use of the animal drug. New evidence raises serious questions about whether the currently approved tolerance for uses of carbadox is adequate under the SOM regulations, and raises serious questions about the continued approval of the compound under the DES Proviso exception to the Delaney Clause due to the lack of a sufficiently sensitive regulatory method.

Carbadox is currently approved based upon CVM's previous conclusion that unextractable residues were QCA related and noncarcinogenic. Given this conclusion and the fact that no residues of carcinogenic compounds were detectable by any method beyond 72 hours, CVM determined that QCA was an acceptable marker residue and established the tolerance at 30 ppb. New evidence presented to JECFA in 2003 undermines the conclusion that

all unextractable residues at the withdrawal period are QCA related. As a result, under FDA's SOM regulations, all unextractable residues except for measured residues of QCA must be considered residues of carcinogenic concern (§ 500.82(b)). Under CVM's analysis (Table 1), concentrations of total residues of carcinogenic concern in liver are approximately 30 times higher than the S_m at the approved 42-day withdrawal period and 11 times higher at the approved 70-day withdrawal period (Ref. 3 at pp. 16-17). CVM would expect that total residues of carcinogenic concern would also exceed the S_m when QCA reaches the approved tolerance of 30 ppb in liver. CVM can no longer conclude that when QCA is at or below 30 ppb, the residues of carcinogenic concern are present at or below a concentration that would present no significant increase in the risk of cancer to humans (§ 500.86(c)).

The new evidence indicates that QCA is not an appropriate marker residue for residues of carcinogenic concern and that QCA at 30 ppb in swine liver is not an appropriate tolerance. The new evidence also shows that the approved regulatory method for all approved carbadox NADAs is inadequate under the SOM regulations (part 500, subpart E). The inadequacy of the regulatory method is a basis for withdrawal of approval of all carbadox NADAs under section 512(e)(1)(B) of the FD&C Act. See Sponsored Compounds in Food-Producing Animals; Criteria and Procedures for Evaluating the Safety of Carcinogenic Residues, Proposed Rule, preamble to the proposed SOM regulations II (50 FR 45530 at 45550).

Similarly, these findings demonstrate that carbadox is no longer shown to be safe under the General Safety Clause because residues of carcinogenic concern remain in swine tissue well past the established withdrawal period. Under the General Safety Clause, drug residues must be determined to be safe based on all available evidence. Where a drug is a known mutagenic carcinogen and new evidence shows that unidentified residues of carcinogenic concern are

present at the established withdrawal time, the drug is no longer shown to be safe. See Section III.D.

As stated previously, the new evidence presented to JECFA undermines the previously held conclusion that all unextracted residues are QCA related and noncarcinogenic. Because carbadox is a mutagenic carcinogen, all otherwise unidentified residues are treated as carcinogenic. No evidence has been presented to CVM by Phibro or any other source to show that the unidentified residues are noncarcinogenic or that the residues do not otherwise present a threat to public health. As a result, carbadox is not shown to be safe under the General Safety Clause.

VI. Notice of Opportunity for a Hearing

New evidence regarding carcinogenic residues in edible tissues of swine treated with carbadox raises serious questions about the human food safety of the drug. Therefore, 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 no longer meets the DES Proviso exception to the Delaney Clause and because new evidence demonstrates that carbadox is not shown to be safe under the General Safety Clause.

Therefore, notice is given to Phibro Animal Health Corp., 65 Challenger Rd., Ridgefield Park, NJ 07660, and to all other interested persons, that the Director of CVM 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 part 514 (21 CFR part 514) and under the authority delegated to the Director of CVM, Phibro Animal Health Corp., the sponsor,

is hereby given an opportunity for hearing to show why approval of NADAs 041-061, 092-955, and141-211 should not be withdrawn.

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

The failure of a holder of an approval to file timely a written appearance and request for hearing as required by § 514.200 constitutes an election not to avail himself or herself of the opportunity for a hearing and 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 of 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 Director of CVM.

VII. 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.

VIII. Paperwork Reduction Act of 1995

The collections of information requirements for this document are covered under OMB control numbers 0910-0032 and 0910-0184.

IX. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday, and are available electronically at http://www.regulations.gov. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

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2. JECFA, Report on Carbadox, 2003. Available at ftp://ftp.fao.org/ag/agn/jecfa/vetdrug/41-15-carbadox.pdf (accessed on March 19, 2016).

3. FDA, Memorandum to the File, Claycamp, H. G., "Preliminary Risk Characterization: Cancer Risk Estimation from Carbadox Residues in Pork from Swine Treated with Carbadox," December 16, 2014.

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10. JECFA, Report on Carbadox, 1990. Available at ftp://ftp.fao.org/ag/agn/jecfa/vetdrug/41-3-carbadox.pdf (accessed on March 19, 2016).

11. FDA, Memorandum to the File, from Division of New Animal Drugs to Director, Bureau of Veterinary Medicine, regarding NADA 41-061, Carbadox for Swine (July 7, 1972).

12. FDA, Memorandum to the File, Approval of Original New Animal Drug Application NADA 92-955 (July 29, 1975).

13. Citizen Petition, Center for Science in the Public Interest, Docket No. FDA-1986-P-0299 (formerly 86P-0212), May 9, 1986.

14. FDA, Response to Citizen Petition, Center for Science in the Public Interest, Docket No. FDA-1986-P-0299 (formerly 86P-0212), May 30, 1995.

15. FDA, Memorandum to the File, from Residue Evaluation Branch, Division of Chemistry to Director, Division of Chemistry, regarding Review of Carbadox Metabolism (September 7, 1994).

16. FDA, Freedom of Information (FOI) Summary, NADA 041-061, MECADOX 10 (carbadox) Type A medicated article, supplemental approval October 5, 1998. Available at http://www.fda.gov/AnimalVeterinary/Products/ApprovedAnimalDrugProducts/FOIADrugSummaries/ucm064223.htm (accessed on March 19, 2016).

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Dated: April 6, 2016.

Tracey Forfa,

Acting Director,

Center for Veterinary Medicine.

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