Submitted: July 11, 2016

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

IN THE MATTER OF NOTICE OF OPPORTUNITY FOR HEARING: PROPOSAL TO WITHDRAW APPROVAL OF NEW ANIMAL DRUG APPLICATIONS FOR CARBADOX IN MEDICATED SWINE FEED	))))	Docket No. FDA-2016-N-0832

EXECUTIVE SUMMARY OF THE DATA, INFORMATION, AND ANALYSIS IN SUPPORT OF PHIBRO ANIMAL HEALTH CORPORATION'S REQUEST FOR HEARING

On July 11, 2016, Phibro Animal Health Corporation (Phibro) submitted to the Food and Drug Administration (FDA) the findings of several new studies confirming the safety of carbadox. The following is a summary of the data and information submitted in support of Phibro's position.

On April 12, 2016, the Acting Director of the Center for Veterinary Medicine (CVM) of FDA proposed to withdraw approval for all New Animal Drug Applications (NADAs) providing for the use of carbadox (the active ingredient in Mecadox®) in medicated swine feed. Phibro promptly requested a hearing on the proposed withdrawal. Phibro's submission provides the data, information, and analyses in support of that requested hearing and includes the findings of several new studies confirming the safety of carbadox, which is used to control bacterial diseases in pigs.

In its Notice of Opportunity for a Hearing (NOOH), CVM cites as the legal bases for its proposed withdrawal of carbadox the Delaney Clause and the "General Safety Clause" as set forth in the Federal Food, Drug, and Cosmetic Act. The initial burden is on FDA to put forward new evidence that revises the Agency's previous safety conclusions with respect to the drug. If

genuine and substantial issues of fact exist regarding the sufficiency of the Agency's "new evidence," an evidentiary hearing must be held to resolve the disputed issues.

As set forth more fully in Phibro's submission, new studies conducted by Phibro confirm the safety of carbadox, and therefore refute CVM's proposal to withdraw approval for the use of carbadox in medicated swine feed. At a minimum, these new data and the related discussion in Phibro's response to the NOOH raise genuine and substantial issues of fact that require a hearing pursuant to the regulations. Moreover, because these data overwhelmingly reconfirm that carbadox is safe, and because the consequences of its withdrawal would have a damaging impact on both human and animal health and on the swine industry, FDA should withdraw the NOOH and meet with Phibro regarding these data.

In July 2005, FDA asked Phibro to "submit existing studies or provide new and complete studies that address the relationship of QCA [quinoxaline-2-carboxylic acid] at 30 ppb and carbadox and desoxycarbadox residues, for the use of QCA as the marker residue for surveillance purposes." At that time (and in fact from the time carbadox was approved), FDA had never considered carbadox residues that were bound to an animal's tissues, and therefore not able to be extracted, to be of carcinogenic concern. In 2011, however, FDA took the position that Phibro would be required to characterize *all* carbadox residues, whether or not those residues were bound to the animal's tissue.

Phibro was surprised by FDA's new demand, which presented daunting analytical challenges. Indeed, it was not clear when FDA made its request that it was even possible to do what FDA demanded. Moreover, the need to do such studies was not clear, as molecules that are so tightly bound to tissues that they effectively cannot be cleaved and extracted without taking

extraordinary measures are also not digestible when the tissue is ingested. In other words, residues that are tightly bound to tissues through covalent bonding cannot act as carcinogens.

Despite these challenges, Phibro has succeeded in meeting FDA's new demands. The newly completed studies, performed by scientists from Charles River Laboratories and the University of Edinburgh, utilized well-established scientific methods to extract and analyze carbadox residues far beyond any level previously achieved. The work conducted by Phibro over the past 4+ years used an advanced Total Radioactive Residue technology and extraction techniques that were adapted for the specific purpose of answering FDA's questions -- namely, to extract and characterize all carbadox bound residues. During these studies, no carcinogenic carbadox-derived residues were detected in meat from animals treated as directed with carbadox. Scientists were able to extract ***100%*** of the residues present at the end of the 42-day FDA-approved withdrawal period and determined there are no harmful residues present (*i.e.*, no carbadox or desoxycarbadox). In addition, these studies categorically confirmed that the carbadox-derived residues that remain at the end of the 42-day withdrawal period comprise tissue-bound QCA (a harmless, non-carcinogenic metabolite of carbadox), thus refuting the FDA's allegations that the bound residues are presumed to be carcinogenic and that QCA is not an appropriate marker. In other words, these studies show (and reconfirm FDA's previous determinations) that carbadox is safe.

FDA points to several pieces of data and information in support of its proposal to withdraw carbadox, namely, references from 1990/1991 authored by Baars, *et al*., JECFA data from 2003 and a 2009 paper by Boison, *et al*. In each such case, Phibro has been able to show that the references on which FDA relies do not demonstrate that carbadox is unsafe and, at a

minimum, Phibro's analysis of these references, Phibro's own studies, and the expert opinions presented in Phibro's submission, raise genuine and substantial issues of fact.

The 1990/1991 Baars, *et al*. references do not present evidence that carbadox is unsafe. Those references show that desoxycarbadox, a carbadox residue, is available in liver at 2 ppb at 10 days and 1 ppb at 14 days post-treatment. The slope in Baars, *et al*. representing how carbadox is metabolized suggests that desoxycarbadox depletes to below 0.915 ppb (the level FDA has determined to be safe for desoxycarbadox in pig liver) on or about 15 days post-treatment, well before the 42-day withdrawal period. Accordingly, even if FDA's contention is that Baars' data reflect "new evidence," that evidence confirms that carbadox is safe. Additionally, the Baars, *et al*. data confirm QCA is an appropriate regulatory marker and align well with the data on which the FDA established the currently approved carbadox withdrawal period.

FDA cites the 2003 JECFA report for the proposition that QCA is not an appropriate marker for carbadox because when QCA reaches the FDA-approved tolerance of 30 ppb in porcine liver, the desoxycarbadox residues exceed 0.915 ppb, the FDA-approved safe level. Phibro has now been able to show that information related to QCA in the JECFA report is unreliable by showing that the data presented were clearly outliers that did not match the very consistent data generated before and since that time, including data FDA reviewed in 1998. In addition, Phibro has been able to show that the JECFA desoxycarbadox levels, when compared with reliable QCA levels generated in 1998 and 2008, support QCA as an appropriate marker for carbadox.

FDA relies on the 2009 Boison, *et al*. paper to support its assertion that questions have been raised about whether QCA is an appropriate marker for carbadox and desoxycarbadox. An

examination of that paper, however, reveals that there were several methodological flaws in Boison, *et al*.'s study and that FDA has incorrectly interpreted the study. Specifically, Boison, *et al*.'s method lacked the critical steps necessary to extract and detect QCA from pigs to which carbadox had been administered. The Boison reference, in fact, has no effect on the evaluation of QCA as a marker for carbadox and desoxycarbadox and FDA's reliance on Boison raises a genuine and substantial issue of fact.

FDA alleged in the NOOH that Phibro had not provided the additional data regarding carbadox safety that the Agency had requested. FDA's requests for data have evolved over time and required Phibro (and the laboratories with which it was working for the past 4+ years) to extract and analyze carbadox residues far beyond any level previously achieved. Phibro has finally been able to extract 100% of the bound residues and determine that no hazardous residues (carbadox or desoxycarbadox) exist at the end of the 42-day withdrawal period. Phibro has also characterized these residues to show that they are safe.

Phibro's studies not only directly refute FDA's allegations that the bound residues are presumed to be carcinogenic and that QCA is not therefore an appropriate marker, but they in fact confirm that carbadox is safe. It is also important to note that the removal of carbadox will have serious health and economic consequences.

Carbadox is not used at all in human medicine, nor is it or its drug class classified as medically important in human medicine, making it highly preferred for the treatment of animal diseases. Withdrawal of carbadox would be contrary to public health objectives regarding responsible antibiotic use because it would likely lead to increased use of alternate animal antibiotics that are classified as medically important for humans, and increase the likelihood of difficult-to-control antimicrobial resistance in important bacterial pathogens. Withdrawal of

carbadox is contrary to objectives of the current FDA antimicrobial initiative. Through Guidance for Industry (GFI) #209 and #213, FDA plans to ensure judicious use of "medically important" antimicrobials used to treat human disease by the end of 2016. There is no ideal or sustainable therapeutic or preventative substitute for carbadox.

The unavailability of carbadox has had serious adverse consequences in other countries that should not be replicated in the United States. Indeed, a recent survey of swine veterinarians in the United States demonstrates that those experts are opposed to the removal of carbadox. In the survey, veterinarians involved in the health decisions for a majority of the swine in the U.S. expressed concern that removal of carbadox would increase animal diseases, including *Salmonella*, swine dysentery and *E.coli*. The veterinarians estimate that removal of carbadox would lead to the deaths of more than one million pigs per year.

The removal of carbadox from the marketplace will also result in significant cost to the American economy and is expected to increase the cost to the swine industry in providing safe meat. It is estimated that the total cost to the U.S. swine industry in the first year carbadox is removed from the market could be as high as $200 million dollars, driven by an increase in enteric diseases, including increased *Salmonella*, swine dysentery and *E.coli*. It is anticipated that the annual costs will continue to grow to approximately $345 million per year.

Carbadox has been safely used in the U.S. for more than 40 years. No harmful residues have ever been found in food when carbadox is used as approved. Phibro's new studies went further than ever before to confirm the product's safety. Phibro's new scientific evidence as to the safety of carbadox is so overwhelming that the NOOH should be withdrawn. At a minimum, Phibro is entitled to a hearing to resolve the numerous genuine and substantial issues of fact identified in this submission.