United States Department of Agriculture

Food Safety and Inspection Service

1400 Independence Avenue, SW, Washington, D.C. 20250

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Ryan Talbott
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Dear Mr. Talbott:

The Food Safety and Inspection Service (FSIS) has completed its review of the petition you submitted on behalf of the Center for Food Safety (CFS) on December 4, 2019, and assigned petition number 19-06. The petition requests that FSIS make certain changes to the National Residue Program (NRP) to provide additional information to the public and other Federal agencies on the frequency and levels of drug residues in or on meat, poultry, and egg products in the United States. Specifically, the petition requests that FSIS: 1) test for residues of all drugs approved for use in food animals in the United States; 2) adopt detection and analysis methods that allow for the lowest limits of detection (LOD) for each compound; 3) set the LOD for compounds in specific tissues from specific species as the threshold for recording a positive residues result; 4) establish clear definitions and parameters for minimum levels of applicability (MLA); and 5) revise annual reporting mechanisms to provide information on all detected residues and their levels, if quantified, that were present on meat, poultry and egg products, regardless of whether the levels detected exceed MLA's or FDA action levels or tolerances. According to the petition, such action is necessary to "protect the health and welfare of consumers" as required by the Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 *et seq*.), the Poultry Products Inspection Act (PPIA) (21 U.S.C. 451 *et seq*.), and the Egg Products Inspection Act (EPIA) (21 U.S.C. 1031 *et seq*.) (the Acts).

The NRP is an important component of FSIS's mission to protect the health and welfare of consumers by ensuring that meat, poultry, and egg products that enter commerce, are safe, wholesome, and not adulterated or misbranded. The range of chemical compounds evaluated for inclusion in the NRP is comprehensive. As noted in your petition, under the NRP, FSIS conducts testing for approved and unapproved veterinary drugs, pesticides, and environmental contaminants known or suspected to be present in food animals. Under the Federal Food Drug and Cosmetics Act (21 U.S.C. 301 *et seq*.), the Food and Drug Administration (FDA) is authorized to establish tolerances, regulatory limits, and other limitations or specifications for animal drugs, approve food additives including conditions under which they may be used, and establish tolerances and regulatory limits for added

or naturally occurring poisonous or deleterious substances, and the Environmental Protection Agency (EPA) is authorized to establish tolerance levels for registered pesticides. FSIS partners with the FDA and the EPA to decide which chemical compounds to test for within each category based on the level of public health concern presented by a compound. FSIS, FDA, and EPA meet to discuss residue results and future NRP proposals at least on an annual basis.

Because FSIS's laboratory resources are limited, any actions intended to address the presence of veterinary drug or other chemical compounds in or on meat, poultry, and egg products need to be targeted to identify potential public health concerns. The changes to the NRP requested in your petition would require that FSIS allocate significant resources to sample, detect, and report veterinary drugs in FSIS-regulated products without considering the human health risk associated with a particular drug or the impact that the changes would have on sampling for other potentially harmful chemical compounds. This change would not be an efficient allocation of Agency resources. As discussed below, the current procedures for identifying, prioritizing, analyzing, and reporting chemical residues under the NRP allow FSIS to effectively address the presence of veterinary drugs and other chemical compounds that could potentially adulterate meat, poultry, or egg products in a manner that is consistent with Agency resources and priorities. Therefore, we are denying your petition without prejudice.

We address the specific actions requested in your petition and respond to what you believe to be limitations of the NRP below.

Animal Drugs Selected for Testing

The petition asserts that FSIS's testing for veterinary drug residues under the NRP fails to sufficiently protect public health because the NRP does not test for all approved animal drugs. According to the petition, because FSIS residue protocols do not require testing for residues of several approved animal drugs that may be routinely used in food animals, the public and federal government are unable to determine the extent and frequency of acute and chronic human exposure to multiple drug residues. The petition states that veterinary drugs that may be used routinely or continuously should be of high priority and provides a list of 13 veterinary drugs approved for extended or continuous use that are not included in the FSIS's testing under the NRP. The petition also asserts that because FSIS does not test for all approved veterinary drugs, there could be risks from exposure to several drug residues simultaneously. To support this assertion, the petition references a study in which retail samples of meat and poultry tested positive for three or more of the veterinary drugs that the products were tested for. The petition also states FSIS should only utilize the best available testing methods and notes that methods for many untested drugs are available, including multi-residue methods using liquid chromatography—tandem mass spectrometry (LC-MS/MS).

FSIS response: We disagree with the assertion that the NRP must include testing for all approved veterinary drugs. The purpose of the NRP is to ensure that FSIS-regulated products that receive

the mark of inspection are free from unsafe residues that violate an FDA or EPA tolerance or that render the product otherwise unfit for human food (21 U.S.C. 601(m)(2), 21 U.S.C. 453(g)(2), 21 U.S.C. 1033(a)(2)). In addition, the NRP supports the regulatory missions of EPA (with regard to pesticide regulation) and FDA (with regard to veterinary drug regulation) by gathering residue data and detecting potential misuse of these chemicals. The NRP surveillance sampling program, i.e., scheduled sampling, is a statistical program. Sampling is done to provide some assurance of detection of a violation that affects a given percentage of the sample population.[1]

FDA is the expert Agency primarily responsible for the regulation of veterinary drugs in the United States through its drug approval and tolerance-setting processes. FSIS consults closely with FDA to decide which drugs to include in its testing methods and how sensitive the tests should be. FSIS defers to FDA in determining that drug residues that are within an FDA tolerance are safe. FSIS finds no public-health need to quantify test results that are below the tolerance level because the presence of veterinary drugs at levels below the tolerance would not render products adulterated under the Acts. FDA is also the agency responsible for taking follow-up regulatory action in response to violative drug residue findings. FSIS's drug surveillance program is designed to support FSIS's and FDA's regulatory and enforcement priorities.

Carcasses at FSIS-inspected establishments are not released into commerce until all test results that bear on the determination whether the carcass is adulterated have been received (see *Not Applying the Mark of Inspection Pending Certain Test Results*, 77 FR 73401, Dec. 10, 2012). When any level of a veterinary drug is detected in a carcass sample, FSIS inspection program personnel are instructed to withhold the mark of inspection from that carcass and condemn the carcass and all parts, unless a tolerance level has been set for the chemical in the tissue and production class in question and the detected level does not exceed this tolerance (see *Residue Sampling, Testing and Other Verification Procedures under the National Residue Program for Meat and Poultry Products*, FSIS Directive 10,800.1, Mar. 3, 2014). If an FSIS-regulated product containing violative veterinary drug residues enters commerce, FSIS takes actions to remove the product from commerce, such as requesting that the producing establishment recall the product. If an establishment refuses to recall a product that contains violative residues, FSIS is authorized to detain and seize the product (21 U.S.C. 672 and 673, 21 U.S.C. 467(a) and 467(b), 21 U.S.C. 1048 and 1049).

While FSIS is not responsible for conducting or managing pesticide or veterinary drug risk assessments, the petition correctly notes that FSIS has worked with EPA in the past to make changes to FSIS's detection capabilities and testing procedures to provide data that better meet EPA's regulatory needs related to pesticides. Similarly, FSIS has worked closely with FDA to

[1] See Appendix III, "Number of Samples Required to Detect Violations with Predefined Probabilities" in the FSIS "Red Book" Available on the FSIS website at: https://www.fsis.usda.gov/science-data/data-sets-visualizations/residue-chemistry

ensure that the NRP meets FDA's regulatory needs and will continue to give serious consideration to requests from FDA on how to maintain or increase the usefulness of the NRP in supporting FDA's regulation of veterinary drugs. If the CFS believes that the FDA needs additional residue testing data to oversee approval and use of veterinary drugs, properly assess cumulative exposure from multiple drugs, or otherwise inform regulation of veterinary drugs, the CFS should consult with the FDA. FSIS is willing to work with FDA to provide data to inform FDA's regulatory decisions with respect to veterinary drugs.

As mentioned above, FSIS testing for all approved veterinary drugs would not be an efficient allocation of Agency resources. Testing priorities are informed by scientific and public health considerations, consultation with FDA (the lead regulatory agency for veterinary drugs), and technical and instrument capabilities. Funding and resource availability are other important factors.

With respect to the issues raised concerning routine or continuous use of veterinary drugs, as well as potential exposure to several drug residues simultaneously, as mentioned above, FSIS coordinates with other agencies on at least an annual basis to review the list of chemical compounds it assesses, and these types of issues are considered as part of that interagency review. Specifically, representatives from FSIS, FDA, EPA, and other Federal agencies, including the USDA Agricultural Research Service (ARS) and Agricultural Marketing Service (AMS) and the Centers for Disease Control and Prevention (CDC) meet at least once a year as part of the Surveillance Advisory Team (SAT). The SAT creates the annual residue sampling plan (per calendar year) using sample results from the NRP, information that the agencies have accumulated during investigations, and information from veterinary drug inventories that FDA has compiled during on-farm visits. The agencies create a list of chemical compounds for testing and rank them using mathematical equations that include variables for public health risk and regulatory concern. In addition to establishing a relative ranking for the chemicals, the SAT determines the compound/production class pairs of public health concern and evaluates FSIS laboratory capacity and analytical methods to devise a final sampling plan. FSIS publishes the final sampling plan in the *National Residue Program Sampling Plan,* which is traditionally referred to as the Blue Book. We intend to present your petition at the next annual SAT meeting to consider some of the issues raised.

With respect to the petition's request for FSIS to use the best available testing methods, each year FSIS improves and modernizes its analytical technologies. Most recently, FSIS adopted a next-generation, multi-residue screening method to strengthen its ability to detect animal drug residues, "Screening and Confirmation of Animal Drug Residues by UHPLC-MS-MS (CLG-MRM3.00).[2] The method is an improvement over the previous multi-residue method (CLG-

[2] FSIS Enhances Residue Testing Constituent Update, August 30, 2019 at: https://www.fsis.usda.gov/sites/default/files/import/ConstiUpdate08302019.pdf

MRM1.08), due to the use of more sensitive instrumentation. In this new analytical method, FSIS increased the number of animal drug residues analyzed in samples. The new method includes some of the most commonly used coccidiostats, such as lasalocid, monensin, narsin, and salinomycin. FSIS is currently working on a more formal prioritization scheme for adding veterinary drugs to the NRP, similar to what has been developed and published for pesticides.

Testing Methods, Limits of Detection, Minimum Level of Applicability

In addition to requesting that FSIS test for all approved veterinary drugs, the petition states that FSIS should use detection and analysis methods that provide for the lowest LOD for each compound and refer to the LOD to determine whether a sample has screened positive for a veterinary drug residue instead of the Agency's MLA. The petition states that FSIS's MLAs for veterinary drugs are based on regulatory tolerance levels set by FDA for specific species and tissues and are generally set at half the FDA tolerance level. According to the petition, identifying positive results based on the MLA rather than the lowest LOD substantially limits the understanding of positive rates and levels of drug residues that are actually present on meat, poultry, and egg products in the United States. To support this assertion, the petition references a study that analyzed samples from 240 pork products and detected ractopamine in approximately 50 samples.

The petition also requests that FSIS establish clear definitions and parameters for MLAs. According to the petition, FSIS's MLAs for veterinary drugs are not consistently established as one-half the tolerance set by FDA, and FSIS does not consider residues above the MLA but below FDA's tolerance to be violative. The petition also states that FSIS datasets for 2016-2017 include positive residue results that are below the established MLA in certain cases. The petition asserts that it is unclear how FSIS uses MLAs for reporting data and taking regulatory action on veterinary drug residues.

FSIS response: The Minimum Level of Applicability (MLA) is a term used in residue chemistry methods to indicate the lowest level at which a method has been successfully validated for a residue in a given matrix and tissue (meat and poultry muscle, kidney, or liver, and processed egg products). It also refers to the lowest level at which a laboratory analyst is expected to maintain ongoing proficiency in the method. In 2011, the MLA for residues was implemented by the FSIS laboratory system to replace the term "Minimum Proficiency Level" (MPL). MPL referred only to analyst proficiency and did not necessarily take method validation into account. Having a method validated prior to use is a fundamental requirement for both regulatory analysis and ISO 17025 compliance, so the MLA became a straightforward way to demonstrate that the method had been validated and that the analyst maintains proficiency. Other regulatory laboratories may use different terms, as there is no standardized language that is recognized globally.

As noted in the petition, FSIS's MLAs for veterinary drugs are not consistently established as one-half the tolerance set by FDA. This is because the MLA is not a regulatory limit; it is a limit established based on the data generated during the method validation. When validating a method for a veterinary drug that has an established level of interest, such as a tolerance or action level, the laboratory typically aims to validate the method at one-half tolerance. The outcome of the validation study then guides at what level the MLA for each analyte/matrix combination is actually set. When no fixed regulatory level has been established (i.e., there is no tolerance or action level for residues typically because any level of residue detected would render the carcass adulterated), the laboratory validates the method at a level which is above the "noise" level of the instrumentation, yet low enough that residues can be detected. The MLA is always set above the LOD (level of detection) and/or LOQ (level of quantitation). The LOD and LOQ are estimated values that can fluctuate depending on several technical factors, such as instrumentation, experimental design, and analyst performance. Thus, FSIS uses the MLA for residues rather than the LOD to ensure confidence and reproducibility for the levels at which the Agency quantifies and reports veterinary drug residues.

With respect to the study that detected ractopamine in pork samples referenced above, the petition notes that most of the detected residues were at levels below 5 ppb, which is well below FSIS's MLA of 25 ppb for swine muscle. FSIS notes that ractopamine has a tolerance of 0.05 ppm (50 ppb) in swine muscle, as listed in 21 CFR 556.570. FDA has the regulatory jurisdiction for setting these tolerances. Any levels of ractopamine found in swine muscle at 50 ppb or higher would exceed the FDA tolerance and would render the carcass adulterated. FDA has determined that concentrations of ractopamine, or any other veterinary drug, below the applicable tolerance level are safe for human consumption and are consistent with approved use of the drug. As the purpose of the NRP is to ensure the safety of the meat, poultry, and egg product supply and to support FDA's mission to prevent veterinary drug misuse, reporting low-level residues below an FDA tolerance is not a focus of the NRP. However, FSIS does report non-violative positives that are greater than the MLA, but less than the tolerance.[3] If the CFS has concerns regarding the current FDA tolerance for ractopamine or any other tolerance for veterinary drug residues in meat poultry or egg products, it may petition the FDA to reconsider these tolerances.

[3] See the FSIS "Red Book" Available on the FSIS website at: https://www.fsis.usda.gov/science-data/data-sets-visualizations/residue-chemistry. As part of increasing transparency, FSIS provides an accompanying excel spreadsheet with residue sampling results, includes detailed information regarding samples taken by FSIS in both the residue domestic scheduled and inspector-generated sampling programs, in addition to the residue import sampling program results. The detailed results include sample collection and review dates, the project code, the animal class, tissue type, chemical residue name, concentration value, sample results (whether positive non-violative or positive violative), chemical concentration values (if any) and the CFR reference per chemical listed in the data sheet.

Reporting Drug Residue Results

Finally, the petition requests that FSIS revise annual reporting mechanisms to provide information on all detected residues and their levels, if quantified, that were present in or on meat, poultry, and egg products. The petition asserts that the FSIS Red Book does not include complete details of the number of positive residue samples for each year because it only provides information on specific drug residues detected if they were detected at violative levels (that is, above FDA tolerances or action levels or above the MLAs for residues with no tolerance or action level). According to the petition, the Red Book should also include specific compounds that had positive, non-violative test results and the levels at which they were present.

The petition also states that while information on non-violative positive results can be found in datasets available on the FSIS website, the information in the data sets is incomplete. The petition describes instances where, according to the petition, the number of positive non-violative and positive violative samples reported in the FY2016 and FY2017 Red Book exceeded the number of positive violative and non-violative samples included in the data sets for those years.

FSIS response: FSIS's current reporting process for residues does what the petition requests: it reports all confirmed residues, both violative and non-violative, in meat, poultry, or egg product. As discussed below, FSIS is also confident that the NRP data is complete and believes that the petition's interpretation is the result of a misunderstanding of the NRP.

For example, the petition states that "[a]ccording to the 2016 Red Book, in FY2016 there were 50 total samples (all species) with positive residues in the domestic scheduled sampling and 3,649 positive samples from the inspector-generated sampling, regardless of whether or not the levels were violative. In total, between these two sampling programs, 3,699 samples were positive for residues." This is an incorrect interpretation of the FSIS inspector-generated test results. The inspector-generated sampling involves FSIS inspectors conducting an in-plant Kidney Inhibition Swab (KIS™) test, a generic colorimetric inhibition test performed at the establishment, when they suspect that animals may have violative levels of chemical residues.[4] If the KIS™ test is negative, the carcass may continue to be retained for additional testing if other drug or chemical residues are suspected; otherwise, the carcass is released to the establishment. If the KIS™ test is positive, the carcass is retained by FSIS pending further testing by an FSIS field laboratory. However, only a fraction of samples that screened positive using the KIS test are actually confirmed as positive after testing by the laboratory. Under the inspector-generated program in FY 2016, 182,184 KIS™ tests were conducted on suspect animals, and 3,649 samples were submitted to FSIS field laboratories for further analysis. Of these, 1,621 (893 violative and 728 non-violative) chemical residues were reported. When added to the 26

[4] FSIS's KIS™ test method can be found at: https://www.fsis.usda.gov/node/1990

violative and 24 non-violative positives from the domestic scheduled sampling, this results in a total of 1,671 positive samples, not 3,699 as stated in the petition.

It should also be noted that the datasets FSIS makes public on its website list 1,679 positive sample results. The eight additional data points are the result of multiple analytes detected in individual animals, but in different tissues of that animal (for example, a sulfamethazine violation in both muscle and liver was reported as one violation in the Redbook, but both violations are posted separately in the data sheet).

For FY2017, similar arguments can be made for the Red Book reports and accompanying excel data sheet.

For the reasons discussed above, we are denying your petition. Because our denial is without prejudice, the CFS is not precluded from submitting a revised petition that contains additional information to support the requested actions. In accordance with our petition regulations, we have posted your petition on the FSIS website (9 CFR 392.6). We intend to post this response as well.

Sincerely,

Rachel Edelstein
Assistant Administrator
Office of Policy and Program Development