



June 5, 2003

Mr. Philip S. Derfler
Deputy Administrator
Office of Policy, Program Development,
and Evaluation
USDA, Food Safety and Inspection Service
350 E, JLW Bldg.
Washington, D.C. 20250

Dear Mr. Derfler,

Thank you for your inquiry concerning the basis for the establishment of action levels and tolerances by FDA. In order to clarify our response, I would like to make a distinction between an action level advisory and an FDA tolerance. An action level advisory is generally made on request by and to FSIS where there has been no new animal drug submission made by a sponsor. As such an action level represents our best effort to establish the concentration of a substance, usually elemental or a natural toxin, below which we have no concerns about the safety of the substance. However, these action levels are not codified and do not have the legal standing of a tolerance.

Conversely, a tolerance is established through analysis of data submitted by a new animal drug sponsor and is codified. Currently, a tolerance represents the concentration of an indicator (the marker analyte) of the total residues in an edible tissue (the target tissue), below which we have a reasonable certainty that no harm will occur to a consumer through daily exposure over a lifetime to the total residues in any edible tissue derived from the medicated food animal. A tolerance may be established for any edible tissue, dependent on the data submitted and requests made by the sponsor of the new animal drug, but must be established for the edible tissue (typically that from which the new animal drug residues deplete the slowest) which can assure the safety of all edible tissues derived from that animal.

In the history of the FDA, there have been several operational approaches imposed on residues of food animal drugs in order to meet the mandated human food safety risk standard of "a reasonable certainty of no harm." It should be emphasized that this is the same standard in place today, and has consistently driven the setting of tolerances for new animal drugs. All tolerances in the CFR are driven by safety considerations and have a toxicological basis. However, as will be described below, the approach used in establishing the tolerance has changed over the years.

The first approach, which was used until the 1970s, was one of "zero tolerance" or "no residues" based upon detectable residues by a regulatory method, which is self-

explanatory and was technology-limited. Neither target animal suitability nor efficacy considerations played a role in the establishment of the "zero" residue level. Toxicology studies and appropriate safety factors were used to assure that the sensitivity of the analytical method used to assure "no residues" was sufficient to provide a reasonable certainty of no harm for consumption of the food product.

A second approach developed as science and technology progressed and the ability to detect residues improved and drove the "no residue" concentration down. A National Academy of Sciences (NAS) evaluation was contracted by EPA and FDA to address the issue of tolerances. In 1965, the NAS recommended the use of "negligible residues" or "permissible residues." This concept was routinely in use by FDA in the 1970s to address food animal drug residues when the supporting toxicological data were limited to sub-chronic (90-day) studies. This approach was based on the assumption that the residue would be present at an insignificant level. The safety of the residue was supported by only limited toxicological data. The negligible residue tolerance was determined as 5% of the acceptable daily intake (as calculated from the toxicological no effect level (NOEL) and a 100-fold safety factor) resulting in what was essentially a 2000-fold safety factor applied to the toxicological NOEL. In addition, an upper limit of 0.1 parts per million (0.1 ppm) was generally imposed on the residues of any non-carcinogenic new animal drug on the basis that more than that would not be "negligible." Higher (finite) tolerances could be established when there were chronic toxicology data supporting that number. The negligible residue approach continued to be used until the early 1980s, at which time it was essentially replaced by the finite tolerance approach.

The establishment of a finite tolerance has been operational for all new animal drugs except carcinogens since the early 1980s. It is based on an analysis of the potential hazard of the residues of a drug product in edible food animal tissues as determined through more extensive toxicological data provided by the drug sponsor. In addition to the 90-day sub-chronic studies typically submitted for a negligible residue tolerance, drug sponsors provide data on developmental toxicity, reproductive toxicity, mutagenicity, and often include chronic exposure data.

At about the same time negligible residues were in place and finite tolerances were beginning to be applied, the concept of establishing the safety of a drug based upon the total residue (the parent drug and its metabolites) and the use of a target tissue to monitor the safety of the entire carcass began to be used.

A separate approach is used for carcinogens that are regulated under the Delaney Clause and the DES Proviso, and subject to the Sensitivity of the Method (SOM) regulation (21 CFR 500.80). This approach is still current and has been used for the withdrawal of approval of DES in 1978, the withdrawal of Nitrofurans in 1991, and the 1998 supplemental approval of carbadox in swine.

As you can see from the above, while there has been a progression in the operational approach for establishing human food safety over the years, the tolerances codified in the CFR today all meet our mandated risk standard of "reasonable certainty of no harm." As such, each represents that concentration of marker analyte below which the residue may

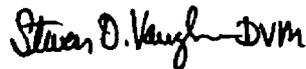
be considered safe for human consumption, and above which we cannot conclude that there is a reasonable certainty of no harm. If an edible tissue exceeds the tolerance, by definition the animal from which it was derived is adulterated and not fit for human consumption.

Considerations of target animal suitability and efficacy have never played a direct role in establishing FDA tolerances. Prior to the amendment of the Federal Food Drug and Cosmetic Act by the Animal Drug Availability Act of 1996, the intended use of the new animal drug was indirectly considered through a general policy that limited a tolerance (otherwise supported by the toxicological data) to no more than that needed based on the residues resulting from the approved use of the new animal drug.

Every tolerance in the CFR has been established through analysis of data submitted by the individual drug sponsors. If a drug sponsor thinks that the current tolerance for residues of their product is too low and wishes to supplement a currently approved new animal drug application in order to obtain a higher tolerance, we will review their data. The responsibility for taking this initiative rests with the drug sponsor, not with FDA.

We would be happy to meet with representatives of your office to discuss this issue. In particular, it may be helpful for representatives of FSIS to interact with staff from the CVM Division of Compliance and FDA Office of Chief Counsel to discuss any concerns FSIS may have about supporting a legal action against illegal residues of an older new animal drug. Please feel free to contact me directly on this matter at 301-827-1796 or Mark Robinson, Division Director, Division of Human Food Safety, at 301-827-5282.

Sincerely yours,



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Office of New Animal Drug Evaluation
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