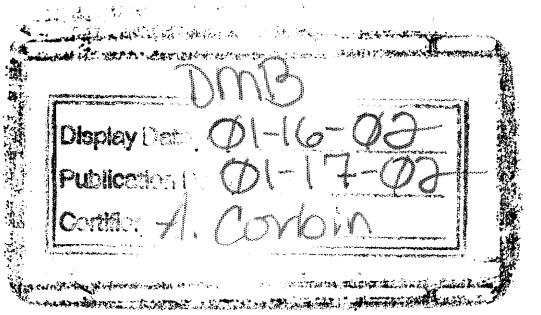

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 500

[Docket No. 01N–0401]

Revision of the Definition of the Term "No Residue"

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend its regulations regarding carcinogenic compounds used in food-producing animals. Specifically, FDA is deleting the operational definition of the term "no residue" and is making conforming amendments to other parts of these regulations. FDA is proposing these amendments in response to a legal opinion issued by the Department of Justice (DOJ), Office of Legal Counsel, which concluded that the operational definition of "no residue" is not legally supportable.

DATES: Submit written or electronic comments on the proposed rule by [*insert date 90 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

FOR FURTHER INFORMATION CONTACT: Steven D. Brynes, Center for Veterinary Medicine (HFV–151), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301–827–6975.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of October 31, 1985 (50 FR 45530), FDA issued a proposed rule implementing the diethylstilbestrol (DES) proviso of the Delaney clause in sections 409, 512, and 721 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 348, 360b, and 379e). The DES proviso provides that we (FDA) can approve an animal feed or color additive or a new animal drug that induces cancer if we find that "no residue" of such additive or drug "will be found (by methods of examination prescribed or approved by the Secretary by regulations * * *), in any edible portion of such animals after slaughter." See e.g., 21 U.S.C. 360b(d)(1)(I). We issued final regulations based on the 1985 proposal in the **Federal Register** of December 31, 1987 (52 FR 49572).

The final rule, which was codified in part 500 (21 CFR part 500) in §§ 500.80 to 500.92, included an operational definition of "no residue" in § 500.84. That definition provides that FDA will consider that "no residue" of a carcinogenic compound remains in the edible tissue of treated animals when the "concentration of the residue of carcinogenic concern in the total diet of people will not exceed S_o." Section 500.82 defines S_o as "the concentration of the test compound in the total diet of test animals that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million." Section 500.82 further provides that FDA will assume that the "S_o will correspond to the concentration of residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to people." Therefore, under these regulations, it is possible for a residue detected by the method approved by FDA to be considered "no residue" if the detectable residue is below the level that corresponds to a maximum lifetime risk of cancer in the test animals of 1 in 1 million ("insignificant risk" or "no significant risk" level).

In the final rule of December 31, 1987, we explained the rationale for this operational definition of "no residue." The preamble to the final rule stated:

Application of * * * the "DES Proviso," hinges therefore on the finding of "no residue" of the substance in edible products.

As a practical matter, however, FDA has been unable to conclude that no trace of any given substance will remain in edible products. The new procedures, therefore, provide an operational definition of "no residue." That is, the procedures are designed to permit the determination of the concentration of residue of a carcinogenic compound that presents an insignificant risk of cancer to the consuming public. That concentration corresponds to a maximum lifetime risk of cancer to the test animal on the order of 1 in 1 million. Thus, the procedures provide for a quantitative estimation of the risk of cancer presented by the residues of a carcinogenic compound proposed for use in food-producing animals. "No residue" remains in food products when conditions of use, including any required preslaughter withdrawal period or milk discard time, ensure that the concentration of the residue of carcinogenic concern in the total diet of people will not exceed the concentration that has been determined to present an insignificant risk.

On October 13, 1995, the DOJ, Office of Legal Counsel, responding to questions posed by the Environmental Protection Agency and FDA, issued a legal opinion entitled "The Food and Drug Administration's Discretion to Approve Methods of Detection and to Define the Term 'No Residue' Pursuant to the Federal Food, Drug, and Cosmetic Act" (DOJ Opinion on FDA Implementation of the DES Proviso) (Ref. 1). Specifically, the opinion addressed the following questions: (1) Whether the FDA has the discretion to refuse to permit the use of an additive in animal feed if the agency finds that there is no method that can "reliably measure and confirm" the presence of residues of carcinogenic concern at and above the "no residue" level for such residues, (2) whether the FDA must revise its regulations to adopt more sensitive methods when they become available once the agency has approved a method of detection, and (3) whether the FDA has the discretion to determine that an edible tissue contains "no residue" when a method of detection reveals the presence of residues of carcinogenic concern that is below the "no significant risk" level.

With respect to the first question, the opinion determined that FDA is under no obligation to approve at least one method for the detection of a residue of a carcinogenic animal food additive and that it has the discretion to refuse to permit the use of unsatisfactory detection methods. In so concluding, the DOJ further stated that FDA may use the "no significant risk" level (defined in § 500.84) as a benchmark for rejecting analytical methods. These conclusions are consistent with FDA's current interpretations of the DES proviso regarding analytical methods.

The second question asks whether FDA must revise its regulations to adopt the "best available" methods for the detection of carcinogenic residues or whether it has discretion to continue to accept results from less sensitive methods. The DOJ asserted that, although one interpretation of the proviso could allow the best available method approach, the statute does not compel that course of action. Thus, the opinion concluded that the statute does not require FDA to replace currently approved methods with more sensitive methods as they become available. Once again, this conclusion agrees with the position taken by FDA.

In considering the third question, the DOJ reasoned that "[g]iving 'no residue' its ordinary meaning, the detected presence of any residue by an approved method would be incompatible with a finding of 'no residue,' and thus would preclude a finding that the [DES] proviso applies." Furthermore, the opinion stated that "[t]here is nothing * * * to suggest that a finding of 'no residue ' could be based upon the detected presence of residue, however insignificant * * *."

DOJ's conclusion that "FDA may not accept a finding that residue is present, but below the 'no significant risk' level, as satisfying the statutory requirement of 'no residue,'" contradicts FDA's present operational definition of "no residue" issued in § 500.84. Therefore, we are proposing amendments to the regulations to make them consistent with the DOJ legal opinion.

II. Description of the Proposed Rule

The agency is proposing to revise the regulations to delete the operational definition of "no residue." Therefore, for a substance to be approved under the DES proviso, no residue can be detectable by the approved regulatory method; that is, any residue in the target tissue must be

nondetectable or below the limit of detection (LOD) of the approved regulatory method. Inasmuch as: (1) The regulatory method currently is defined in § 500.82 as the aggregate of all experimental procedures for measuring and [emphasis added] confirming the presence of the marker residue in the target tissue, and (2) FDA must, for regulatory and scientific reasons, be capable of identifying the detected residue with a high degree of certainty, FDA is proposing to define the LOD, for the purposes of this rule, as the lowest concentration of analyte that can be confirmed by the approved regulatory method.

The agency is proposing the following conditions that a sponsor of a carcinogenic compound must satisfy with respect to the sponsor's proposed regulatory method. First, the sponsor must provide a method that is at least capable of reliably quantitating residues at and above the R_m (the concentration of marker residue that the regulatory method must be capable of measuring in the target tissue), which we will continue to calculate in the manner provided in the current regulations in §§ 500.80 to 500.92. Therefore, FDA will use the "no significant risk" level determined through appropriate toxicological testing as a benchmark for assessing the acceptability of a regulatory method. Second, under the proposed regulations, a sponsor must provide sufficient data to permit us to estimate the LOD of the method as defined above and in proposed § 500.82. Given the first requirement, the LOD will likely be below the R_m, and consequently, the LOD will replace the R_m as the "no residue" determinant.

Under the proposed regulations, we have defined the LOD as the lowest concentration of analyte that can be confirmed by the approved regulatory method. Believing that there are several valid procedures to estimate the LOD, we have chosen not to specify in this proposed rule any one specific procedure or protocol as a standard requirement for establishing the LOD. Therefore, under the proposed rule, we would consider and evaluate any reasonable, generally recognized procedure that is consistent with the aims and requirements of regulatory exposure estimation and risk assessment practices of FDA.

III. Environmental Impact

The agency has carefully considered the potential environmental impacts of this proposed rule. The agency has determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IV. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121)), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity).

The Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities, if the rule may have a significant impact on a substantial number of small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 (Public Law 104–4) requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million in any one year (adjusted annually for inflation).

The agency concludes that this proposed rule is consistent with the principles set forth in the Executive order and in these two statutes. The agency expects only very slight, if any, compliance costs to result from the proposed rule. Companies have requested approvals for carcinogenic compounds under the current regulation in only a few cases since it was published as a final rule in 1987, probably at least in part because of concerns over public acceptance of such products. We anticipate that, for the same reasons, companies will rarely request approvals for carcinogenic compounds under a final version of the proposed rule. As a result, the proposed

rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. Further, we certify that the proposed rule would not have a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for the proposed rule, because the proposed rule is not expected to result in any 1-year expenditure that would exceed $100 million adjusted for inflation. The current inflation-adjusted statutory threshold is about $110 million.

We are proposing to amend the regulations regarding the carcinogenic compounds used in food-producing animals by deleting the operational definition of "no residue." Under the proposed rule, for a carcinogenic compound to be approved, no residue of the compound can be detectable using an approved regulatory method. Any residue in the target tissue would have to be nondetectable or below the LOD.

As stated previously, we are making this change in response to a DOJ opinion that the current operational definition of "no residue" is not legally supportable. The benefit of this change would be an increase in the clarity of the current regulations concerning carcinogenic compounds used in food-producing animals.

The deletion of the definition is not expected to impose any measurable compliance costs on the sponsors of compounds that are submitted to us for approval as new animal drugs or feed or color additives. The submission of data to meet the requirements of the proposed rule will be in place of, and nearly identical to, data that were submitted to meet the operational definition of "no residue." We do not expect a noticeable increase in the level of effort expended in preparing a submission. To the extent that incremental compliance costs exist, we believe them to be inconsequential. In theory, another result of this proposal might be the possible increase in the withdrawal period for some number of compounds submitted for approval, which would represent some loss of value to the sponsor. However, because we anticipate very few requests for approval

of new animal drug applications or feed additives under the provisions of the proposed rule, we believe any loss of value would be insignificant.

As stated above, the Regulatory Flexibility Act requires agencies to examine regulatory alternatives for small entities, if the rule may have a significant economic impact on a substantial number of small entities. Since we have determined that the possible compliance costs to any sponsor would be extremely small, if they occur at all, we are certifying that the proposal would not have a significant economic impact on a substantial number of small entities. No further small business analysis is required.

V. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the proposed rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VI. Paperwork Reduction Act of 1995

The information collected in § 500.88 has been approved by the Office of Management and Budget (OMB) under OMB control number 0910–0032. This proposed rule amends § 500.88, but does not substantively modify the information collection. Therefore, clearance by OMB under the Paperwork Reduction Act of 1995 is not required.

VII. Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this proposal by [*insert date 90 days after date of publication in the* **Federal Register**]. Two copies of any comments are to be submitted, except that individuals

may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

VIII. Reference

The following reference has been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. U.S. Department of Justice, "The Food and Drug Administration's Discretion to Approve Methods of Detection and to Define the Term 'No Residue' Pursuant to the Federal Food, Drug, and Cosmetic Act: Memorandum Opinion for the Assistant Administrator and General Counsel Environmental Protection Agency and the General Counsel Department of Health and Human Services," October 13, 1995.

List of Subjects in 21 CFR Part 500

Animal drugs, Animal feeds, Cancer, Labeling, Packaging and containers, Polychlorinated biphenyls (PCB's).

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 500 be amended as follows:

PART 500—GENERAL

1. The authority citation for 21 CFR part 500 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 342, 343, 348, 351, 352, 353, 360b, 371, 379e.

§ 500.80 [Amended]

2. Section 500.80 *Scope of this subpart* is amended in paragraph (a) by removing the phrase "provides an operational definition of no residue and".

§ 500.82 [Amended]

3. Section 500.82 *Definitions* is amended in paragraph (b) by alphabetically adding "*Limit of Detection (LOD)* means the lowest concentration of analyte that can be confirmed by the approved regulatory method."; by removing from the definition of "*Marker residue*" the phrase "permitted concentration" and by adding in its place "S_m"; by removing from the definition for "*Preslaughter withdrawal period or milk discard time* " the phrase "for the residue of carcinogenic concern in the edible product to deplete to the concentration that will satisfy the operational definition of no residue" and by adding in its place "at which no residue is detectable in the edible product using the approved regulatory method (i.e., the marker residue is below the LOD)"; by removing from the definition of "R_m" the phrase "in the last tissue to deplete to its permitted concentration"; and by revising the definition of "S_m" to read "S_m means the concentration of residue in a specific edible tissue corresponding to a maximum lifetime risk of cancer in the test animals of 1 in 1 million.".

4. Section 500.84 is amended by revising the section heading, by adding two sentences at the end of paragraph (c)(1), by revising paragraph (c)(2), and by adding paragraph (c)(3) to read as follows:

§ 500.84 Conditions for approval of the sponsored compound.

* * * * *

(c) * * *

(1) * * * Because the total diet is not derived from food-producing animals, FDA will make corrections for food intake. FDA will designate as S_m the concentration of residue in a specific edible tissue corresponding to a maximum lifetime risk of cancer in test animals of 1 in 1 million.

(2) From the appropriate residue chemistry data FDA will calculate the R_m as described in § 500.86(c). The sponsor must provide a regulatory method in accordance with § 500.88(b). FDA will calculate the LOD of the method from data submitted by the sponsor under § 500.88. The LOD must be less than or equal to R_m.

(3) FDA will conclude that the provisions of this subpart are satisfied when no residue of the compound is detectable (that is, the marker residue is below the LOD) using the approved regulatory method under the conditions of use of the sponsored compound, including any required preslaughter withdrawal period or milk discard time.

5. Section 500.88 is revised to read as follows:

§ 500.88 Regulatory method.

(a) The sponsor shall submit for evaluation and validation a regulatory method developed to monitor compliance with this subpart.

(b) The regulatory method must be able to confirm the identity of the marker residue in the target tissue at a minimum concentration corresponding to the R_m. FDA will determine the LOD from the submitted analytical method validation data.

(c) FDA will publish in the **Federal Register** the complete regulatory method for ascertaining the marker residue in the target tissue in accordance with the provisions of sections 409(c)(3)(A), 512(d)(1)(H), ~~and (i),~~ and 721(b)(5)(B) of the act.

Dated: 1/3/02

January 3, 2002.

Margaret M. Dotzel,
Associate Commissioner for Policy.

[FR Doc. 01–????? Filed ??–??–01; 8:45 am]

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