

Preslaughter withdrawal period or *milk discard time* means the time after cessation of administration of the sponsored compound at which no residue is detectable in the edible product using the approved regulatory method (i.e., the marker residue is below the LOD).

Regulatory method means the aggregate of all experimental procedures for measuring and confirming the presence of the marker residue of the sponsored compound in the target tissue of the target animal.

R_m means the concentration of the marker residue in the target tissue when the residue of carcinogenic concern is equal to S_m .

Residue means any compound present in edible tissues of the target animal which results from the use of the sponsored compound, including the sponsored compound, its metabolites, and any other substances formed in or on food because of the sponsored compound's use.

Residue of carcinogenic concern means all compounds in the total residue of a demonstrated carcinogen excluding any compounds judged by FDA not to present a carcinogenic risk.

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.

S_o means 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. For the purpose of this subpart, FDA will also assume that this 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.

Sponsor means the person or organization proposing or holding an approval by FDA for the use of a sponsored compound.

Sponsored compound means any drug or food additive or color additive proposed for use, or used, in food-producing animals or in their feed.

Target animals means the production class of animals in which a sponsored compound is proposed or intended for use.

Target tissue means the edible tissue selected to monitor for residues in the target animals, including, where appropriate, milk or eggs.

Test animals means the species selected for use in the toxicity tests.

Threshold assessment means FDA's review of data and information about a sponsored compound to determine whether chronic bioassays in test animals are necessary to resolve questions concerning the carcinogenicity of the compound.

[52 FR 49586, Dec. 31, 1987, as amended at 67 FR 78174, Dec. 23, 2002]

§ 500.84 Conditions for approval of the sponsored compound.

(a) On the basis of the results of the chronic bioassays and other information, FDA will determine whether any of the substances tested are carcinogenic.

(b) If FDA concludes that the results of the bioassays do not establish carcinogenicity, then FDA will not subject the sponsored compound to the remainder of the requirements of this subpart.

(c) For each sponsored compound that FDA decides should be regulated as a carcinogen, FDA will analyze the data from the bioassays using a statistical extrapolation procedure.

(1) For each substance tested in separate bioassays, FDA will calculate the concentration of the residue of carcinogenic concern that corresponds to a maximum lifetime risk to the test animal of 1 in 1 million. FDA will designate the lowest value obtained as S_o . 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 .

§ 500.86

(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.

[52 FR 49586, Dec. 31, 1987, as amended at 67 FR 78174, Dec. 23, 2002]

§ 500.86 Marker residue and target tissue.

(a) For each edible tissue, the sponsor shall measure the depletion of the residue of carcinogenic concern until its concentration is at or below S_m .

(b) In one or more edible tissues, the sponsor shall also measure the depletion of one or more potential marker residues until the concentration of the residue of carcinogenic concern is at or below S_m .

(c) From these data, FDA will select a target tissue and a marker residue and designate the concentration of marker residue (R_m) that the regulatory method must be capable of measuring in the target tissue. FDA will select R_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 and, therefore, that the residue of carcinogenic concern in the diet of people does not exceed S_o .

(d) When a compound is to be used in milk- or egg-producing animals, milk or eggs must be the target tissue in addition to the tissue selected to monitor for residues in the edible carcass.

(Approved by the Office of Management and Budget under control number 0910-0228)

§ 500.88 Regulatory method.

(a) The sponsor shall submit for evaluation and validation a regulatory method developed to monitor compliance with FDA's operational definition of no residue.

(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 deter-

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mine 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)(I), and 721(b)(5)(B) of the act.

(Approved by the Office of Management and Budget under control number 0910-0228)

[52 FR 49586, Dec. 31, 1987, as amended at 67 FR 78174, Dec. 23, 2002]

§ 500.90 Waiver of requirements.

In response to a petition or on the Commissioner's own initiative, the Commissioner may waive, in whole or in part, the requirements of this subpart except those provided under § 500.88. A petition for this waiver may be filed by any person who would be adversely affected by the application of the requirements to a particular compound. The petition shall explain and document why the requirements from which a waiver is requested are not reasonably applicable to the compound, and set forth clearly the reasons why the alternative procedures will provide the basis for concluding that approval of the compound satisfies the requirements of the anticancer provisions of the act. If the Commissioner determines that waiver of any of the requirements of this subpart is appropriate, the Commissioner will state the basis for that determination in the regulation approving marketing of the sponsored compound.

(Approved by the Office of Management and Budget under control number 0910-0228)

§ 500.92 Implementation.

(a) This subpart E applies to all new animal drug applications, food additive petitions, and color additive petitions concerning any compound intended for use in food-producing animals (including supplemental applications and amendments to petitions).

(b) This subpart E also applies in the following manner to compounds already approved:

(1) For those compounds that FDA determines may induce cancer when ingested by man or animals, i.e., suspect