under conditions of use reasonably certain to be followed in practice. This subpart identifies the steps a sponsor of a compound shall follow to secure the approval of the compound. FDA guidance documents contain the procedures and protocols FDA recommends for the implementation of this subpart. These guidance documents are available from the Division of Dockets Management (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Requests for these guidance documents should be identified with Docket No. 1983D–0288.

(b) If FDA concludes on the basis of the threshold assessment that a sponsor shall conduct carcinogenicity testing on the sponsored compound, FDA will also determine whether and to what extent the sponsor shall conduct carcinogenicity testing on metabolites of the sponsored compound. The bioassays that a sponsor conducts must be designed to assess carcinogenicity and to determine the quantitative aspects of any carcinogenic response.

(c) If FDA concludes on the basis of the threshold assessment or at a later time during the approval process that the data show that the sponsored compound and its metabolites should not be subject to this subpart, FDA will continue to consider the compound for approval under the general safety provisions of the act for risks other than cancer.

(d) This subpart does not apply to essential nutrients.

[52 FR 49586, Dec. 31, 1987, as amended at 59 FR 14365, Mar. 28, 1994; 62 FR 66983, Dec. 23, 1997; 65 FR 56480, Sept. 19, 2000; 67 FR 78174, Dec. 23, 2002; 68 FR 24879, May 9, 2003; 69 FR 17292, Apr. 2, 2004]

§ 500.82 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this subpart.

(b) The following definitions apply to this subpart:

Act means the Federal Food, Drug, and Cosmetic Act (sections 201–901, 52 Stat. 1040 *et seq.* as amended (21 U.S.C. 301–392)).

Essential nutrients means compounds that are found in the tissues of untreated, healthy target animals and not produced in sufficient quantity to support the animal's growth, development, function, or reproduction, e.g., vitamins, *essential* minerals, *essential* amino acids, and *essential* fatty acids. These compounds must be supplied from external sources.

FDA means the Food and Drug Administration.

Limit of detection (LOD) means the lowest concentration of analyte that can be confirmed by the approved regulatory method.

Marker residue means the residue selected for assay whose concentration is in a known relationship to the concentration of the residue of carcinogenic concern in the last tissue to deplete to its S_m.

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 a residue of carcinogenic concern in a specific edible tissue corresponding to no significant increase in the risk of cancer to the human consumer. For the purpose of § 500.84(c)(1), FDA will assume that this S_m will correspond to the concentration of residue in a specific edible tissue that corresponds to a

maximum lifetime risk of cancer in the test animals of 1 in 1 million.

S_o means the concentration of a residue of carcinogenic concern in the total human diet that represents no significant increase in the risk of cancer to the human consumer. For the purpose of § 500.84(c)(1), FDA will assume that this S_o will correspond to the concentration of 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.

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; 77 FR 50593, Aug. 22, 2012]

§ 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 either analyze the data from the bioassays using a statistical extrapolation procedure as outlined in paragraph (c)(1) of this section or evaluate an alternate procedure proposed by the sponsor as provided in § 500.90. In either case, paragraphs (c)(2) and (3) of this section apply.

(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.

(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; 77 FR 50593, Aug. 22, 2012]

§ 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