4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 500

[Docket No. FDA-2010-N-0612]

Animal Drugs, Feeds, and Related Products; Regulation of Carcinogenic Compounds in Food-Producing Animals

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations regarding compounds of carcinogenic concern used in food-producing animals. Specifically, the Agency is clarifying the definition of "S_o" and revising the definition of "S_m" so that it conforms to the clarified definition of S_o. Other clarifying and conforming changes are also being made.

DATES: This rule is effective [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

On December 20, 2010, FDA issued a proposed rule (75 FR 79320) to amend its regulations regarding compounds of carcinogenic concern used in food-producing animals. Specifically, the Agency clarified the definition of "S_o" and revised the definition of "S_m" so that it would conform to the clarified definition of S_o. The Agency also proposed a number of clarifying and conforming changes.

The Federal Food, Drug, and Cosmetic Act (the FD&C Act) contains three anticancer, or Delaney, clauses: Sections 409(c)(3)(A), 512(d)(1)(I), and 721(b)(5)(B)(i) (21 U.S.C. 348(c)(3)(A), 360b(d)(1)(I), and 379e(b)(5)(B)(i)), pertaining to food additives, new animal drugs, and color additives, respectively. These clauses prohibit approval of substances that have been shown to induce cancer in man or animals. However, each clause contains an exception, termed the "Diethylstilbestrol (DES) Proviso," that permits administration of such substances to food-producing animals where: (1) The food additive, color additive, or new animal drug will not adversely affect the animal and (2) no residue of the food additive, color additive, or new animal drug will be found in any edible portion of that animal by a method of examination prescribed or approved by the Secretary of Health and Human Services by regulation. The regulations under part 500 (21 CFR part 500), subpart E entitled "Regulation of Carcinogenic Compounds Used in Food-Producing Animals" (§§ 500.80 through 500.92), implement the DES Proviso. To elaborate on how to determine that there is no residue, and thus demonstrate that the second prong of the DES Proviso has been satisfied, the regulations define several terms, including S_o and S_m.

S_o is currently defined as the concentration of the compound of carcinogenic concern in the total diet of test animals that corresponds to a maximum lifetime risk of cancer to the test animals of 1 in 1 million, and is calculated from tumor data of the cancer bioassays using a statistical extrapolation procedure. The definition of S_o also provides that FDA will assume that the S_o corresponds 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. The concentration, derived from the S_o, of residues of carcinogenic concern in a specific edible tissue is termed the S_m.

This rule changes the definition of S_o so that it is primarily defined as "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 * * *" and secondarily as "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." The change in this rule to the definition of S_o is intended to enable the Center for Veterinary Medicine to consider allowing the use of alternative procedures to satisfy the DES Proviso (See 75 FR 79320 at 79321) without requiring the development of a second, alternative, set of terminology. FDA believes that the original intent of 21 CFR part 500, Subpart E, as reflected in the preamble to the final rule establishing that regulation, was to place an emphasis on no significant increase in the risk of cancer to the human consumer, rather than on the specific 1 in 1 million risk of cancer to the test animals approach (See e.g., 52 FR 49572 at 49575 and 49582). Therefore, FDA has concluded that the redefinition of S_o is consistent with this original intent of the regulation.

For clarification purposes, FDA is also redefining S_m in § 500.82 to conform this definition with the redefinition of S_o as described previously. Specifically, S_m will mean 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. However, the definition of S_m will also retain the existing reference to a maximum lifetime risk of cancer in the test animals of 1 in 1 million.

Finally, FDA is amending § 500.84(c) to clarify that for each compound that is regulated as a carcinogen, FDA will analyze the data submitted using either a statistical extrapolation procedure as provided in § 500.84(c)(1) or an alternate approach as provided in § 500.90.

FDA's goal in these changes is to clarify that the terms S_o and S_m apply even when the alternative procedures provided for in § 500.90 are used to satisfy the DES Proviso, not to alter the usual process for approving compounds of carcinogenic concern. As such, in the absence of a waiver of the requirements of § 500.84(c)(1), FDA maintains that sponsors must meet the conditions for approval set for in § 500.84, including the default approach of a 1 in 1 million lifetime risk to the test animal.

II. Comments

FDA received six comments in response to the proposed rule. Two of these comments were outside the scope of the rule as they advocated in one case that FDA hold a public hearing regarding the drug Avastin®, and the other comment concerned veterinary compounding.

(Comment 1) Of the remaining comments, one generally supported the rule, but mistakenly believed that the rule "will limit carcinogenic compounds in food producing animals to 1 in 1 million."

In fact, the rule clarifies the definition of S_o in 21 CFR 500.82 to mean primarily "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 * * *" and secondarily, "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." The rule also clarifies the definition of S_m to mean primarily "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 * * *" and secondarily "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."

(Comment 2) A comment from a veterinary association generally supported the rule and its goal to allow the use of alternative procedures to satisfy the DES Proviso without requiring the development of a second, alternative, set of terminology. The comment advocated the use of "statistically valid risk assessment procedures in its evaluation and consideration of the compounds of carcinogenic concern." The comment continued, "That if alternative procedures are allowed, they should be also definable and data driven." FDA generally agrees with the comment that an alternative procedure should be definable and data driven in order to be acceptable. However, the recommendation is also outside the current scope of the current rule as it clarifies the definition of S_o and S_m and will not address alternative procedures.

(Comments 3 and 4) Another commenter opposed the rule, advocating a ban on all carcinogens in animal food, even in minute quantities. A second comment mistakenly stated that the rule "is a proposal to remove any carcinogen from any drugs or feed that are given to animals that are generally eaten by humans."

As previously stated, the FD&C Act contains three anticancer, or Delaney, clauses: Sections 409(c)(3)(A), 512(d)(1)(I), and 721(b)(5)(B)(i), pertaining to food additives, new animal drugs, and color additives, respectively. These clauses prohibit approval of substances that have been shown to induce cancer in man or animals, with the following exceptions termed the "DES

Proviso." The DES Proviso permits FDA to approve carcinogenic compounds for use in food-producing animals if it concludes that, when used in accordance with its label directions: (1) The compound will not adversely affect the animal; and (2) "no residue" of the compound will be found in any edible portion of the animals using a method of detection prescribed by FDA. FDA's approach to implement the Delaney clause and the DES Proviso is described in part 500, subpart E, entitled "Regulation of Carcinogenic Compounds Used in Food-Producing Animals," §§ 500.80 through 500.92. As described earlier, the current rule clarifies the definitions within this set of regulations.

III. Environmental Impact

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 final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct 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 Agency believes that this final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. FDA concluded that the

proposed rule would not impose any direct or indirect costs on industry or government through the changes to the definitions of S_o and S_m and to § 500.84(c), but rather would clarify these definitions to enable FDA to consider using alternative procedures to satisfy the DES Proviso without requiring the development of a second, alternative, set of terminology. FDA did not receive any public comments that challenged this conclusion. As such, FDA certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $139 million, using the most current (2011) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

V. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the 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

This final rule refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in § 500.84 have been approved under OMB control number 0910-0032.

List of Subjects in 21 CFR part 500

Animal drugs, animal feeds, Cancer, Labeling, Packaging and containers, Polychlorinated biphenyls (PCBs).

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 500 is 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.

2. In § 500.82(b), revise the definitions of "S_m" and "S_o" to read as follows:

§ 500.82 Definitions.

* * * * *

(b) * * *

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.

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3. In § 500.84, revise paragraph (c) introductory text to read as follows:

§ 500.84 Conditions for approval of the sponsored compound.

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(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.

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Dated: August 17, 2012.

Leslie Kux,

Assistant Commissioner for Policy.

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