DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 510 and 558

[Docket Nos. 76N-0172 and 76N-0232]

Nitrofurans; Withdrawal of Approval of New Animal Drug Applications

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule; final decision following a formal evidentiary public hearing.

SUMMARY: The Commissioner of Food and Drugs is issuing his final decision on the proposal to withdraw approval of the new animal drug applications (NADAs) for two nitrofuran animal drugs: furazolidone (NADAs 11-698, 9-073, 12-061, 9-393, 13-805) and nitrofurazone (NADAs 6-395, 8-142, 9-415, 8-989, 10-741). The drugs are labeled and approved for antiprotozoal use for a wide variety of conditions in poultry and swine.

The Commissioner has determined that nitrofurazone and furazolidone are not shown to be safe under the conditions of use for which they were approved under 21 U.S.C. 360b(e)(1)(B).[1] Additionally, the Commissioner finds that furazolidone and its metabolites have by substantial new evidence been shown to induce cancer in man or animals within the meaning of 21 U.S.C. 360b(d)(1)(I). Thus, he is withdrawing approval for the drugs and is revoking the regulations codifying the approval of these applications in 21 CFR 510.515, 558.4, 558.15, and 558.262, and 558.370. Also, he is affirming with modifications the initial decision of the Administrative Law Judge, who made similar findings.

EFFECTIVE DATE: September 23, 1991.

ADDRESSES: The transcript of the hearing, evidence submitted, and all other documents cited in this decision may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, from 9 a.m. to 4 p.m., Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Robert L. Spencer, Division of Regulations Policy (HFC-220), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3480.

SUPPLEMENTARY INFORMATION: The purpose of this proceeding is to determine whether the Food and Drug Administration (FDA) should withdraw approval of the NADAs for use in food-producing animals. The effect of this decision is that these two drugs may no longer be marketed in the United States, nor may they be exported except as allowed by law.

I. Introduction

The history of this hearing is set forth in the initial decision (I.D.) and in the notice of hearing (49 FR 34965, September 4, 1984). That entire history will not be repeated here. Briefly, this consolidated proceeding involves two animal drugs that have been used in this country since the 1940's, in the case of one of the drugs, and since the 1950's, in the case of the other drug. The two drugs, furazolidone and nitrofurazone, are part of a chemical class referred to as nitrofurans. In the 1960's, evidence first surfaced that furazolidone caused tumors in laboratory animals. As evidence began to mount, FDA issued a notice of opportunity for hearing on March 31, 1971 (36 FR 5927), proposing to withdraw the NADAs for nitrofurazone on the grounds that it was no longer shown to be safe. A similar notice for furazolidone was issued on August 4, 1971 (36 FR 14343).

Since that time, the sponsors of these drugs (Hess and Clark and SmithKline, sponsors) have brought new data before the agency, which has reviewed the data. A full evidentiary hearing has been held to determine whether the NADAs of these two drugs should be withdrawn on the grounds that the drugs are no longer shown to be safe, and, in the case of furazolidone, whether its NADA should be withdrawn under the Delaney anticancer clause as well.

The Administrative Law Judge (ALJ) issued his I.D. on November 12, 1986, finding that the NADAs should be withdrawn. The ALJ found that furazolidone was an animal carcinogen that should be withdrawn under both the Delaney clause (21 U.S.C. 360b(d)(1)(I), as incorporated in 21 U.S.C. 360b(e)(1)(B)) and the general safety clause (21 U.S.C. 360b(e)(1)(B)). He also found that nitrofurazone, including its metabolites, is an animal tumorigen, and, therefore, a suspect carcinogen that should be withdrawn under the general safety clause. The ALJ also found that the sponsors had failed to provide a reliable method of residue detection for either drug and that the residues of neither drug have been shown to be safe. In addition, he determined that the concentrations of residues of furazolidone were not shown to be below the level of carcinogenic or toxicological concern.

Since the issuance of the I.D., the sponsors have filed briefs and exceptions totalling over 350 pages that take exception to virtually every ultimate and supporting conclusion of the ALJ, and that raise several legal and procedural exceptions as well.[2] Following the filing of exceptions, on August 25, 1987, the Center for Veterinary Medicine (Center) moved to reopen the evidentiary record in order to receive National Toxicology Program (NTP) draft reports of bioassays involving nitrofurazone, one of the drugs at issue here, and nitrofurantoin, another nitrofuran but one not directly at issue here.[3] See GF-1700. On September 21, 1987, the two sponsors of the NADAs also filed motions requesting that these materials be admitted in the record, and in addition requesting that the case be remanded to the ALJ for further testimony regarding the issues raised by the NTP reports.

By an order dated November 2, 1987, then Commissioner Frank Young granted the motions by all parties to reopen the record to admit the draft NTP reports. In response to the sponsors' motion to remand the matter for further testimony, Dr. Young permitted a limited remand to the ALJ. Under the terms of the remand, each party was allowed to submit written testimony concerning the NTP reports from one expert witness who had already testified in the proceeding. The remand order also allowed 1 day of cross-examination to be conducted before the ALJ. Finally, the order allowed each party to submit a supplemental brief following the hearing on the NTP reports. Each party filed its expert's supplemental testimony on January 6, 1988. The hearing on remand was held on February 3, 1988, and supplemental briefs were filed on March 8, 1988. Since that time, the record in this hearing has been officially closed.

After fully reviewing the evidence in the administrative record and the exceptions to the I.D. raised by the sponsors, I find that there is clearly enough evidence in the record to justify the ALJ's conclusion that furazolidone and nitrofurazone are no longer shown to be safe.

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[1] Section 360b(e)(1)(B) contains a reference to "subparagraph (H) of paragraph (1) of subsection (d) * * *." Because, in Pub. L. 100-670, Congress redesignated subparagraph (H) as subparagraph (I), the reference should read "subparagraph (I) of paragraph (1) of subsection (d) * * *." For purposes of this final decision, FDA is interpreting the act as if Congress had made this necessary conforming change.

[2] The exceptions filed by the sponsors in this proceeding exceeded in volume those filed in any other hearing before FDA. Many exceptions were frivolous or trivial.

[3] The final version of this report has been published, but it does not differ from the draft as to any conclusions pertinent to this hearing.

I also find overwhelming evidence in the record to support the ALJ's conclusion that the sponsors have failed to provide a reliable means for detecting residues of these drugs and their breakdown products in animal tissue. Such a detection method is necessary to enable FDA to ensure that no dangerous residues enter the human food supply.

On the basis of the administrative record, I find that I am unable to ensure that foods derived from animals treated with these drugs will contain no more than safe levels of residues of furazolidone, nitrofurazone, and their breakdown products (metabolites). Therefore, I am by this notice withdrawing all NADAs for furazolidone and nitrofurazone.

In doing so, pursuant to 21 CFR 12.130(d), I am adopting the I.D. as issued with some modifications as stated below. As to exceptions filed by the parties, I am herein addressing only those that I consider significant. I am not required by law or regulation to address *every* exception made—only those raising "significant" issues. *Simpson* v. *Young*, 854 F.2d 1429, 1434 (D.C. Cir., 1988); 21 CFR 12.120(b) and 12.130(c). Where I do not specifically address an exception of Hess and Clark (H&C) or SmithKline (SK), their exceptions are overruled for reasons stated in the Center's Reply to Exceptions.

I am expressly not ruling on any exception filed by the Center because I believe that doing so is not essential to a decision on the issues in this proceeding. As a result, my failure to address a particular exception by the Center should not be construed as either an affirmance or an overruling of that exception.

II. Initial Findings

1. I reaffirm the statement of the allocation and formulation of the burden of proof in the Commissioner's diethylstilbestrol (DES) decision (44 FR 54852), September 21, 1979) and apply that to this proceeding. Under both the Delaney and general safety clauses, approval may be withdrawn if "new evidence," evaluated together with previously existing evidence, shows that the drug is not shown to be safe. "New evidence" includes any evidence not available at the time the application was approved, tests by new methods, and tests by methods not originally considered applicable. There does not appear to be an issue about the "newness" of the evidence upon which the Center relies. The evidence concerning the nitrofurans was not available at the time they were originally approved.

The proponent of withdrawal, the Center, has the burden of making the first showing (i.e., that the drug is no longer shown to be safe). *Hess and Clark, Division of Rhodia, Inc.* v. *Food and Drug Administration*, 495 F.2d 975, 992 (D.C. Cir. 1974).[4] In *Hess and Clark I*, the court found that FDA has "an initial burden of coming forward with some evidence of the relationship between the residue and safety to warrant shifting to the manufacturer the burden of showing safety." Id. at 993. In the Commissioner's DES decision, Commissioner Kennedy adopted the following formulation of the Center's threshold burden:

> "* * * [the Center] must provide a reasonable basis from which serious questions about the ultimate safety of DES and the residues that may result from its use may be inferred."

44 FR 54861.

Once the limited threshold burden has been satisfied, of course, the burden passes to the sponsors to demonstrate safety. *Id.*

There does not appear to be a significant difference between the parties on the subject of the burden of proof. In any case, I find that the ALJ applied the correct standard.

2. I find that cost/benefit considerations are irrelevant under both the Delaney clause and the general safety clause. I agree with the Center's view that *American Textiles Manufacturers Institute* v. *Donovan*, 452 U.S. 490 (1981) is ample authority for the proposition that clauses like the Federal Food, Drug, and Cosmetic Act's (the act) general safety clause do not permit, much less invite, cost/benefit analysis.[5] The sponsors do not seriously argue that such an analysis would be applicable where the Delaney clause applies.

3. The sponsors argue that the rodent studies that indicted nitrofurans as carcinogens did not satisfy good laboratory practice (GLP) standards and, thus, cannot satisfy even the Center's limited threshold burden of proof. I disagree. No one argues that these studies were very good studies by today's standards. However, despite their faults, as explained below, the data that they generated constitute substantial evidence of carcinogenicity—evidence which is sufficient to satisfy the Center's threshold burden.

I should note that FDA's GLP regulations were not even proposed until several years after the nitrofuran bioassays were completed. Even more important, by the terms of the preamble to the GLP regulations, "valid data and information in an otherwise unacceptable study which are adverse to the product * * * may serve as the basis for regulatory action. This disparity in treatment merely reflects the fact that a technically bad study can never establish the absence of a safety risk but may establish the presence of a previously unsuspected hazard." (November 19, 1976, 41 FR 51206 and 51212). To the same effect, see FDA's similar statement in the preamble to the final rule (43 FR 59990).

The report of the NTP ad hoc panel on chemical carcinogenesis testing and evaluation (HF-104) cannot be cited to the contrary: "All studies must serve as an adequate basis for regulatory decisions even though they have protocol deficiencies in number of animals per group, number of dose levels, absent clinical observations, etc." HF-104, 12-4. The panel added that "our intent is *not* to imply that previous studies would or should be judged inadequate on the basis of modern criteria [emphasis added]." Id. at 13.

4. I need not and do not address the question of whether hormonally mediated carcinogens are subject to the Delaney clause. This is because the sponsors have not proven that any compound that is the subject of this hearing is a hormonally mediated carcinogen. See, e.g., Denial of Petition for Listing of FD&C Red No. 3 (February 1, 1990, 55 FR 3520, 3537, and 3541). See also *infra*, pp. 37 ff. In addition, as discussed elsewhere (i.e., see pp. 48 ff), I find that none of the compounds that are the subject of this hearing has been shown to be safe within the meaning of the general safety clause. 21 U.S.C. 360b(e)(1)(B).

5. I agree with the Center (main brief at 82, n. 67) that 10^{-6} is an appropriate risk standard by which to judge nitrofurans and their metabolites. The sponsors, while not directly attacking this standard, did suggest that FDA has in the past allowed greater levels of risk, but they have cited no FDA-approved new animal drug for which higher levels of risk from residue were found.

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[4] There are two *Hess and Clark* cases: *Hess and Clark, Division of Rhodia, Inc.* v. *Food and Drug Administration*, 495 F.2d 975 (D.C. Cir. 1974) (hereafter *Hess and Clark I*); and *Rhone-Poulenc, Inc., Hess and Clark Division* v. *Food and Drug Administration*, 636 F.2d 750 (D.C. Cir. 1980) (hereafter, *Hess and Clark II*).

[5] In the Commissioner's DES decision, 44 FR at 54883, FDA said: "The law is clear that FDA may not consider socio-economic benefits in the determination of the safety to human beings of a new animal drug, and I am not prepared to conclude that it permits consideration of human health benefits."