DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 76N-0002]

Diethylstilbestrol; Withdrawal of Approval of New Animal Drug Applications; Commissioner's Decision

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The agency is publishing the Commissioner of Food and Drugs' decision, which constitutes his findings of fact and conclusions of law on the issues in a formal evidentiary public hearing, withdrawing approval of new animal drug applications for diethylstilbestrol implants and liquid and dry feed premixes for use in cattle and sheep.

EFFECTIVE DATE: June 29, 1979.

ADDRESS: The transcript of hearing, evidence submitted and all other documents cited in the decision may be seen in the office of the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857, from 9 a.m. to 4 p.m. Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Constantine Zervos, Scientific Liaison and Intelligence Staff (HFY-31), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4490.

SUPPLEMENTARY INFORMATION: Although this document contains minor editorial changes from the original decision, such changes are made only to comply with document drafting guidelines issued by the office of the Federal Register; there are no substantive differences between the document that follows and the official copy of the Commissioner's Decision dated June 29, 1979.

The Commissioner's Decision

As Commissioner of Food and Drugs, I am, pursuant to 21 U.S.C. 360b(e)(1) and the authority delegated to me in 21 CFR 5.1(a)(1), ordering withdrawal of approval of new animal drug applications (NADA's): 10421, 10964, 11295, 11485, 12553, 15274, 31446, 34916, 44344, 45981, and 45982. These NADA's are for diethylstilbestrol (DES) implants and liquid and dry feed premixes for use in cattle and sheep. This action is taken on the basis of the record developed at an administrative hearing held pursuant to 21 U.S.C. 360b(e).

On this day I have also issued an order revoking 21 CFR 556.190. That regulation identified the mouse uterine/paper chromatography method of analysis as the approved method for determining whether DES residues exist in edible tissues of cattle and sheep treated with DES. As discussed below, the adequacy of that or any other method for detecting DES residues was an issue in the evidentiary hearing on the withdrawal of approval of the DES NADA's. The order revoking 21 CFR 556.190 states that nothing in the record of the evidentiary hearing demonstrates that the agency's previously announced decision to revoke that regulation is incorrect. My analysis of the evidence in this record on that issue is contained in this Decision.

The Initial Decision of the Administrative Law Judge who presided at the evidentiary hearing on the withdrawal of the DES NADA's was issued on September 21, 1978. All parites filed exceptions to that decision pursuant to 21 CFR 12.125(a). My decision accords with the Initial Decision insofar as the Administrative Law Judge found that approval of the NADA's must be withdrawn pursuant to the so-called "safety clause" of 21 U.S.C. 360(e)(1)(B) (discussed below). The Administrative Law Judge also found that the Delaney Clause (also discussed below) did not apply to DES because no DES residues have been found in edible tissues by the approved analytical method. I do not reach that issue because I find that the Delaney Clause applies to DES by virtue of the revocation this day of 21 CFR 556.190.

The applicants who sought a hearing on the withdrawal of the DES NADA's are American Home Products Corp., Dawes Laboratories, Inc., Hess & Clark, Division of Rhodia Inc., and Vineland Laboratories, Inc. They have filed joint papers and are referred to as the "manufacturing parties." Nonparty participants favoring continued approval of DES are the American Society of Animal Science, The Pacific Legal Foundation, and the National Cattleman's Association and are referred to as the "intervenors." The Bureau of Foods and the Bureau of Veterinary Medicine of the Food and Drug Administration (FDA) appeared jointly in favor of withdrawal and are referred to as the "Bureaus."

Testimony was submitted in written form, with an opportunity for oral corss-examination. Written testimony was given exhibit numbers. Citations to the record in this Decision are as follows: manufacturing parties' exhibits (M-); Bureaus' exhibits (G-); intervenors' exhibits (PA-, PN-, PP-, PS-,); transcript of cross-examination (Tr. at); entries in administrative (but not evidentiary) record (Record No.); Initial Decision (I.D. at). I also cite to the parties' exceptions. Because the Bureaus' arguments are most fully explained in their brief to the Administrative Law Judge, I sometimes refer to that document.

The manufacturing parties have requested oral argument (Manufacturing Parties' Exceptions at 11). Because I do not find oral argument necessary, I am denying that request, cf. 21 CFR 12.125(e).

This Decision constitutes my findings of fact and conclusions of law on the issues in this hearing and supersedes the initial decision. The statement of the history of this proceeding set out below is, however, taken with only slight modification directly from the Initial Decision.

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I. Introduction

(A) Diethylstilbestrol

DES is one of a class of chemicals known as stilbenes. Stilbenes are not produced metabolically by animals; DES does, however, produce effects similar to those produced by endogenous estrogens (G–189 at 2).

DES is used as a growth promotant in cattle and sheep. It is approved for use as an additive to animal feed, 21 CFR 558.225, and as a subcutaneous ear implant, 21 CFR 522.640. (It is implanted as a pellet of DES, which dissolves over time and thereby provides DES continuously to the animal's circulation.)

DES is a carcinogen in animals. See section II below. This fact has been noted by two different Courts of Appeals, See *Hess & Clark, Division of Rhodia, Inc., v. FDA*, 495 F.2d. 975, 979 (D.C. Cir. 1974); *Chemetron Corp. v. U.S. DHEW*, 95 F.2d, 995, 997 (D.C. Cir. 1974); *Bell v. Goddard*, 366 F.2d. 177, 179 (7th Cir. 1966). The "DES exception" to the Delaney Clause, discussed below, was written precisely because the Congress understood that DES is a carcinogen in animals. See, e.g., 108 Cong. Rec. 21077–83 (1962).

One of the issues in the hearing is stated as follows: "Is DES a carcinogen, and is there a known no-effect level for its carcinogenic properties?" (I.D. at 2). The manufacturing parties do not argue that DES is not a carcinogen (though they never concede that it is). Rather, they argue that "there is a no-effect level below which DES is not associated with carcinogenesis" (Manufacturing Parties' Narrative Statement at 1, Record No. 76). In any case, manufacturing parties' witnesses have stated that DES is a carcinogen, though they argue it is only as carcinogenic as endogenous estrogens (see Manufacturing Parties' Exceptions at 96–97).

The record shows that animal drug use of DES is banned in Canada (M–51 at 29) and in many European countries (M–64 at 24 G–84 at 59). DES was once used as an implant in poultry, but approval of that use has been withdrawn, see *Bell v. Goddard, supra*.

(B) History

The use of DES in feed premixes was first approved in 1954 under section 505 of the Federal Food, Drug, and Cosmetic Act. The approval was based on data that demonstrated that, using the mouse uterine test, no residues could be detected in edible tissue of livestock 48 hours after withdrawal.

Approval for DES implants in cattle also became effective in 1955 on the basis of mouse uterine assay data demonstrating "no residue" under the permitted conditions of use. Applications became effective for DES in sheep feed premixes and implants in 1957 and 1959, respectively.

The current standards for approval of NADA's are set forth in 21 U.S.C. 360b. 21 U.S.C. 360b(d)(1)(H) imposes additional restrictions on the approval of animal drugs that have been shown to cause cancer. Under that section, no drug may be found to be safe if:

> * * * such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal." * *.

This language is the codification in 21 U.S.C. 360b of the anticancer clause that was added to the Federal Food, Drug, and Cosmetic Act by the Food Additives Amendment of 1958. This language is referred to as the "Delaney Clause."

In 1962, Congress amended the Delaney Clause to permit approval of a carcinogen as an animal drug in certain circumstances. As it appears in the present new animal drug provision, the added language is as follows (21 U.S.C. 360b(d)(1)(H)):

> [The Delaney Clause] shall not apply with respect to [a drug that causes cancer] if the Secretary finds that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (c), (d), and (h) [of this section]), in any edible portion of such animals after slaughter or in any foods yielded by or derived from the living animals;" * *

This amendment became known as the "DES exception" because it was enacted with the DES situation in mind. See, e.g., 108 Cong. Rec. 19916–19920 (Sept. 27, 1962). (It has also been referred to as the "DES clause" or the "DES proviso.") In accordance with this amendment, FDA in 1963 issued food additive regulations providing for the use of DES in animal feeds and establishing official methods for detection, identification and measurement of DES residues (28 FR 1507; Feb. 16, 1963).

The official assay method is composed of the mouse uterine assay, which measures total estrogenic activity at 2 parts per billion (ppb), and the paper chromatography assay, which was thought to be capable of differentiating DES from other estrogens at levels above 10 ppb, 21 CFR 556.190. These assays have been approved since 1963.

Since publication of the detection method in 1963, a number of NADA's for the use of DES have been approved by FDA (41 FR 1804; Jan. 12, 1976). In each instance, the agency concluded that if, when the drug was used in accordance with the conditions of use prescribed in the labeling, DES residues could not be detected in edible tissue by the approved method, the requirements of the law were satisfied (id.). As discussed in sections II(A) and III(B), new information about DES and a reevaluation of the data before the FDA at the time the method was approved have now placed this conclusion in question.

Radioactive tracer studies conducted by the United States Department of Agriculture (USDA) in the early 1970's suggested that use of DES under the prescribed conditions of use can result in residues in edible tissues (id.). These radioactive residues were found at levels that are below the sensitivity of

the officially recognized assay methods. (See section III(B)(2).)

On March 11, 1972, FDA published a notice of opportunity for hearing on the proposed withdrawal of approval of NADA's for DES premixes (37 FR 5264; March 11, 1972). On June 21, 1972 (37 FR 12251), a similar notice was issued for both DES premixes and implants under the same provision of the act. The notice stated that the hearing procedures were being invoked in order to develop on the public record the information necessary for a formal decision on DES.

On August 4, 1972 (37 FR 15747), hearings on DES liquid and dry feed premixes were denied on the ground that holders of NADA's failed to demonstrate the presence of genuine and substantial issues of fact. Approval of NADA's for DES premix was therefore withdrawn (37 FR 15749) pursuant to 21 U.S.C. 360b(d)(1)(H) and 360b(e)(1)(B). Final ruling on DES implants was deferred pending receipt of the results of a USDA study.

The USDA radioactive-tagged DES implant study showed the presence of DES residues 120 days after implantation. On the basis of this information, FDA withdrew approval of NADA's for DES implants on April 27, 1973 (38 FR 10485) under 21 U.S.C. 360b(e)(1)(B). The same order denied the requested hearings for lack of genuine issues of material fact.

The manufacturers petitioned for review of the above orders under 21 U.S.C. 360b(h). The United States Court of Appeals for the District of Columbia Circuit reversed FDA's actions on the procedural ground that it was necessary to hold a public hearing before final action could be taken. *Hess & Clark* v. *FDA, supra; Chemetron Corp. v. HEW, supra.* These decisions reinstated the regulations and approvals for DES NADA's.

On March 27, 1974 (39 FR 11299), the FDA proposed to revoke the approved method of analysis for DES (mouse uterine and paper chromatography) on the grounds that this method failed to meet the requirements of accuracy, sensitivity and specificity. On January 12, 1976 (41 FR 1804), the agency responded to the comments on this proposal. On that date it also issued the notice of opportunity for hearing that initiated the present proceeding. The FDA stated that it intended to revoke the methods regulation at the time that it took final action on the notice of opportunity for hearing.

The manufacturing parties requested a hearing and, on November 26, 1976 (41 FR 52105), FDA issued the notice of hearing for this proceeding.

(C) Issues

The issues in this proceeding, as set forth at the February 14, 1977 Prehearing Conference and modified by Order of the Commissioner on March 23, 1977, are as follows (I.D. at 2–3):

(1) Is DES a carcinogen, and is there a known no-effect level for its carcinogenic properties?

(2) Does DES have any adverse biological effects other than carcinogenesis that call its safety into question under the previously approved conditions of use and have safe tolerance levels been established for those effects?

(3) Has the existence of residues in edible tissues resulting from the use of DES been sufficiently established to call its safety into question under the previously approved conditions of use?

(4) Have any residues resulting from the use of DES implants and DES in feed been detected in edible tissues of animals presented for slaughter and are such residues likely to occur when the approved conditions of use are followed?

(5) Are there adequate and reliable methods, that are practicable for regulatory purposes and capable of detecting and identifying residues in edible tissue resulting from the use of DES at all levels above the level taken as the operational definition of no residue, or at all levels above a level established as a safe tolerance for any noncarcinogenic adverse effects, whichever is lower?

(6) Can adequate and necessary conditions for safe use be established?

(7) Is the mouse uterine/paper chromotography mothod, which is the assay currently approved for DES by regulation, adequate and practicable for regulatory purposes and capable of detecting and identifying residues in edible tissues resulting from the use of DES?

(8) If substances resulting from the use of DES under the conditions of use on the basis of which the NADA's were approved present some potential hazard to the public health, do the public health, environmental and economic benefits from the continued use of DES as an animal growth promotant outweigh that potential hazard?

(9) Will the withdrawal from the market of DES for use as an animal growth promotant significantly affect the quality of the human environment?

(D) General Introductory Comments

This Decision is a legal document in which are resolved difficult scientific issues. A few introductory notes may be helpful in understanding the discussion that follows.

First, the Decision discusses what might at first appear to be very small amounts of DES in edible tissues of meat from treated animals. Yet, as a respected cancer expert has testified, we have no data upon which to base the conclusion that any amount of a carcinogen above the single-molecule level would not produce a response (Tr. at 266 (Dr. Shimkin)). (Two ppb DES in 100 grams (slightly less than a quarter of a pound) of liver means that there are 450 trillion molecules of DES in that piece of liver (G–72 at 3).) The risk of cancer would, of course, be expected to be lower the smaller the number of molecules of a carcinogen that are ingested (cf. Tr. at 266).

Second, this Decision draws conclusions from animal tests in which relatively small numbers of animals are fed relatively large amounts of DES. (As discussed below in section III(D)(2)(a) of this opinion, however, some witnesses testified that 6.25 ppb of DES caused mammary tumors in mice in the Cass study.) Because animal tests can of necessity use only a relatively small number of animals (compared to the total U.S. population that eats meat from animals treated with DES), it would take an extremely potent carcinogen to demonstrate a response in an animal test when a substance is administered at the dose level at which humans actually eat that substance. (See, generally, the discussion of this problem at 42 FR 19998 (Apr. 15, 1977).)

A number of considerations are involved in interpreting animal data, and I do not wish to oversimplify that task. But clearly, if one is concerned to detect a substance that, at the dose level at which it is actually consumed, will cause cancer in 1 in 10,000 individuals (about 22,000 cancers in the U.S. population), a test of that substance at that dose level in 100 (or even 1000) animals is not likely to be successful. Even with 10,000 or 100,000 animals, the number of "spontaneous" cancers is likely to obscure the effect of the substance that causes cancer at the rate of 1 in 10,000. For reasons of cost and general practicality, most animal cancer studies are limited to a couple of hundred individual animals per dose level. As explained at 42 FR 19998, scientists generally assume that for cancer and other toxic effects, the amount of an effect is a function of the size of the dose administered although there is controversy about effects of very low doses. For these reasons, it is necessary and appropriate to utilize results from higher dosages in small numbers of animals to compute risks from lower dosages in the human population unless there is some reason not to do so.

(As is discussed in section III(D)(1), the manufacturing parties argue that there are reasons for not making this extrapolation with DES. I explain in detail my reasons for rejecting those arguments at the point in the opinion at which the arguments are discussed.)

Third, the risk associated with DES must be considered in light of the widespread consumption of DES-treated meat. In 1975, over 25 million head of DES-treated cattle (and over 7 million head of DES-treated sheep) were reported slaughtered (G–68 at 3).

Fourth, although there is evidence, discussed below, that DES used as medication in pregnant women causes cancer in some of their female offspring, it is unlikely that any individual will ever be identified as having been afflicted with cancer because he or she consumed meat containing residues of DES in the range of parts per billion. As Dr. Saffiotti pointed out, because our population is inevitably exposed to a variety of carcinogens, it is generally impossible (in the absence of evidence of, for example, occupational exposure to carcinogenic chemicals) to attribute any specific cancer to any specific cause (G–80 at 6). Yet this record warrants a finding that a significant (though unquantifiable) number of the cancers that do occur in this country today are associated with the use of DES in food-producing animals.

II. The Delaney Clause

There is no dispute that DES is a carcinogen when ingested by animals (see discussion above; G–22; G–34 at 1; G–37 at 2; G–46 at 2; G–47; G–59 at 2; G–70 at 2; G–80 at 7–8; G–84; G–85 at 6). As noted above in section I(B), I may not approve (and must withdraw approval of) the NADA for any animal drug that induces cancer when ingested by animals unless that drug comes within the DES exception to the Delaney Clause, 21 U.S.C. 360b(e)(1)(B); (d)(1)(H). A drug comes within the DES exception only if it is found that (1) the animals treated with the drug will not be adversely affected by it and (2) no residue of the drug will be found, by methods prescribed or approved by the Commissioner by regulation, in the edible products of the treated animals, 21 U.S.C. 360b(d)(1)(H).

The Administrative Law Judge found that neither the approved analytical method for DES nor any other analytical method is adequate for use with DES (I.D. at 51). He was not, however, authorized to revoke the regulations setting out the approved analytical method for DES and did not purport to do so. Because, at the time of the Initial Decision, there was an approved method and no residues had been reported by that method, the Administrative Law Judge found that the Delaney Clause had not been shown to apply to DES (I.D. at 13).

For the reasons stated in the following section, I am now revoking the analytical method for DES. My decision to do so is supported by the evidence in the record, discussed in section II(A), that no analytical method is acceptable for DES. Because there is now no approved method of analysis for DES, I conclude that the Delaney Clause applies to the drug. I therefore withdraw approval of the DES NADA's on that ground.

The Bureaus filed exceptions to the Administrative Law Judge's ruling with respect to the Delaney Clause. They argue that, even if the methods regulation were not repealed, the record would nevertheless support withdrawal of approval pursuant to the Delaney Clause under two theories:

First, they argue that the record shows that DES causes adverse effects in cattle (Bureaus' Exception at 7ff). The question whether DES causes adverse effects in animals was not stated as an issue in this hearing, but some evidence that the drug does cause such adverse effects was elicited, primarily during cross-examination of an intervenor's witness (see Tr. at 2056–57; 2067; 2152).

Second, the Bureaus contend that the showing by other analytical methods that DES use causes residues above 2 ppb means that I cannot find that no residues "will be found" by the approved method (Bureaus' Exceptions at 3). Under this theory, the lowest level of detection of the approved method would become, in effect, a tolerance level, and a finding by another (unapproved) method that an animal drug caused residues above the tolerance level would be a basis for invoking the Delaney Clause.

Because I find that the revocation of the analytical methods regulation for DES requires invocation of the Delaney Clause with respect to the DES NADA's. I do not reach the issues raised by the Bureaus' exceptions.

(A) Revocation of the Analytical Method Regulation

(1) *Background.* The regulation prescribing analytical methodology necessary for invocation of the DES exception (21 CFR 556.190) may be revoked pursuant to the notice and comment procedures prescribed in the Administrative Procedure Act, 5 U.S.C. 553(c). Those regulations are specifically exempted by 21 U.S.C. 360b(d)(1)(H)(ii) from the additional requirements of subsections (c), (d), and (h) of 21 U.S.C. 360b.

The approved analytical method for DES residues comprises two independent measurements: measurement of the uterotrophic effect of DES in immature mice and measurement of the migration coefficient of DES by paper chromatography, 21 CFR 556.190. The most recent proposal to revoke the FDA regulation identifying this method as approved was published on March 27, 1974 (39 FR 11299). The proposal stated the agency's conclusion that the approved method was inadequate to satisfy the intent of 21 U.S.C. 360b(d)(1)(H) (the Delaney Clause) because its lowest limit of reliable measurement was not shown to be acceptable, and because there were unanswered questions about its specificity and accuracy. That proposal noted that the approved method was not being used by the Department of Agriculture in its monitoring program.

In the January 12, 1976 (41 FR 1804), notice of opportunity for hearing in this proceeding the FDA summarized, and responded to, the comments received in response to the March 27, 1974 proposal. That document stated that the method would be revoked at the time of final action on the notice of opportunity for hearing (41 FR 1807).

In announcing the decision to revoke the current regulations, the January 12, 1976 notice suggested that a replacement method might be approved if demonstrated to be adequate (id.). No potential replacement, however, is adequate. My analysis of the evidence in the record on this issue with respect to the approved method and the manufacturing parties' proposed replacement, the gas chromatography/mass spectrometry method, follows. (A second potential alternative method, the radio-immunoassay, is not sufficiently well developed for use (G–65 at 2; G–66 at 1–2) and is not relied upon by the manufacturing parties.)

(2) *Lack of Knowledge About Metabolism of DES.* For an NADA to be approvable pursuant to the DES exception to the Delaney Clause, that NADA must contain an analytical method that is capable of assuring that no drug residue of toxicological concern will appear in unsafe levels in edible tissues of treated animals (see G–72 at 7; G–57 at 2). For DES we do not know enough about the residues of toxicological concern to determine that any analytical method would satisfy this requirement.

Any substance that enters an animal body is metabolized (changed) by being broken down into smaller molecules, by binding to other molecules already present in the body, and/or by a combination of breaking down and binding. Therefore, it is expected (and in this case shown by data) that part of the DES administered to cattle and sheep is metabolized into other substances (see, e.g., G–72 at 6–7). Residues of DES in the

edible tissues of cattle and sheep will, therefore, be made up not only of DES itself but also of the metabolites of DES.

The record reveals no testing of the metabolites of DES that would provide a basis for determining which are the metabolites about which one should be concerned from the perspective of public health protection (cf. G–57 at 3). The record provides no data that would allow one to calculate at what level any metabolite that is a carcinogen might be regarded as safe. Even if we knew what the toxicologically important metabolites of DES were and what safe levels of those metabolites were, I could not find any analytical method acceptable on this record. The record provides no information about the rates of depletion of the different DES residues in cattle and sheep. Without that information, I could not determine whether DES itself or any other residue (i.e., a metabolite) of DES was the appropriate substance to be measured by an analytical method. (Generally, a method should detect one "marker" residue, whose absence, as determined by a method having a certain level of sensitivity, assures that the total residue will not be present above a safe level, computed for the total residue upon the basis of testing of its components; see G–24 at 10423 (44 FR 17070, 17095; March 20, 1979).)

As the Administrative Law Judge noted (I.D. at 41), Congress recognized that the safety of an animal drug to human consumers is dependent in part upon their consumption of that drug's metabolites ("any substance formed in or on food because of use of such drug"), 21 U.S.C. 360b(d)(2)(A). As noted, DES residues may include both DES itself and its metabolites. Without knowledge of (1) what the toxicologically important residues of DES are, (2) what levels of these residues may be considered safe, and (3) what the relationship of the various residues of DES to each other is, I cannot responsibly conclude that any analytical method for DES will provide assurance that edible tissues of treated animals will not be hazardous. (See G–72 at 6–7.)

(The manufacturing parties might argue that I do not need information about the metabolites of DES because the approved method would detect not only DES itself but also its metabolites that produce an estrogenic effect (cf. M–110 at 10). There are, however, a number of metabolites of DES that are not known to produce an estrogenic effect (see G–189 at 3–4). I discuss below, as part of the section (section III(D)(1) of this opinion) dealing with the so-called "safety clause," my reasons for rejecting the manufacturing parties' argument that one need be concerned only about the estrogenic effects of DES. Thus, I can not presume that no nonestrogenic metabolite of DES is of public health significance. I cannot, therefore, find that a method able to measure only estrogenic DES metabolites is acceptable.)

The lack of necessary information about the DES residues to be measured is itself a basis for revoking the currently approved analytical method and refusing to approve the gas chromatography/mass spectrometry method proffered by the manufacturing parties as an alternative. Moreover, there are serious faults with each of these methods, which would make them unusable even assuming that DES itself were the only DES residue of concern.

(3) *Inadequacy of the Approved and the Proposed Alternative Method.* The lack of a showing that either the approved analytical method or the gas chromotography/mass spectrometry method detects DES residues at a level low enough so that those residues do not pose a significant risk of cancer is the most important failing of the methods. Each of the deficiencies discussed, however, (except for the deficiency in the approved method with respect to the attribute of specificity) is an independent basis for disapproval of these methods.

(a) *Inadequacy of Approved Analytical Method.* The record in this case supports the FDA's previous decision that the regulation setting out the mouse uterine/paper chromatography method as approved must be revoked. The attributes upon the basis of which a method of analysis is judged include accuracy, dependability, lowest limit of reliable measurement, practicality and specificity (G–26 at 1–2; G–72 at 2, 9–10). For a method to be approved or remain approved by the FDA, each of the method's attributes must be adequate for regulatory purposes.

(i) *Accuracy and Dependability.* The mouse uterine assay requires that the uterine weight of mice fed the liver to be tested be compared to the uterine weight of mice fed control tissues. The proposal to revoke the regulation approving the method noted the possibility that estrogenic substances in the control tissues might cause DES in the tested tissues to go unnoticed. Therefore, a question was raised about the accuracy of the method (39 FR 11300). At the hearing, Bureaus' witness Dr. Rodricks stated his opinion that this method had not been shown to be accurate, but he did not explain the reasons for this statement (G–72 at 9–10).

FDA did not rely upon the lack of accuracy of the approved method in the 1976 decision to revoke the regulations. I do not, on the basis of this record, now rely on the alleged inadequacy of the method with respect to that attribute.

The Bureaus offered no evidence (other than the unexplained opinion of Dr. Rodricks (id.)) that the mouse uterine/paper chromatography method is not dependable. The Bureaus did argue that certain problems—namely, technical and environmental controls and performance time—may affect dependability and accuracy. These problems, however, are matters of practicality and are treated below under the discussion of that attribute. Thus, I do not find the approved method inadequate with respect to the attributes of dependability and accuracy. The mouse uterine/paper chromatography method, however, has been shown to be unacceptable for regulatory purposes with respect to the remaining three attributes.

(ii) *Lowest Limit of Measurement.* The prime attribute of a method, the lowest limit of reliable measurement, is the level (or amount) of the chemical under analysis below which the assay will yield no interpretable results (G–72 at 2). The mouse uterine assay can consistently measure estrogenic activity at the levels of 2 ppb DES equivalents (G–67 at 2; G–72 at 2–3; M–62 at 1; see also M–153 at 1; M–170 at 2). It does not, however, distinguish DES from other estrogens (G–67 at 3; M–62 at 1).

Paper chromatography is used with the mouse uterine assay in an attempt to provide the requisite specificity. Paper chromatography is alleged to be able to distinguish DES from other estrogens at levels equal to, or greater than, 10 ppb (G–72 at 10; cf. M–170 at 2). Assuming that this claim for the paper chromatography method is correct, the lowest level of reliable measurement of the approved method is effectively 10 ppb DES in liver tissues.

The manufacturing parties argue that 2 ppb should be accepted as the lowest limit of reliable measurement of the approved method. They argue, in effect, that if no residue is detected by the mouse uterine assay, one can be assured that no residue of 2 ppb DES or above exists. If a residue is detected by the mouse uterine assay, on the other hand, they argue that "additional samples of tissue can be analyzed by a variety of more specific techniques, such as gas liquid chromatography with mass spectrographic analysis" (M–110 at 11; Manufacturing Parties' Exceptions at 193). This argument, rather than

supporting the current method, in fact suggests that a new combination of assays should be substituted for those currently approved.

In any case, whether the lowest limit of the approved method is 2 ppb or 10 ppb, that limit is not acceptable because there is no basis for concluding that residues below either of those levels will not cause cancer in human consumers. (As the Administrative Law Judge noted, each of these limits is very close to the 6.25 ppb dosage that was reported to have resulted in a carcinogenic effect in the Gass mouse study (G–22) see section III(D)(2)(a)).)

My conclusion that no no-effect level has been shown for the carcinogenic effects of DES is discussed in detail below in section III(D)(2). Bureaus' witnesses Dr. Gross and Dr. Rodricks did calculate, using the Gass study (G–22) data, that no more than 1 part per trillion (ppt) of DES in the diet would be consistent with a risk of 1 cancer in one million consumers (a cancer rate assumed to be "acceptable" or "insignificant" or tantamount to no cancer) (G–34 at 2; G–72 at 4). (Another witness, Dr. Condon, had calculated the same figure from the Gass data, but did not purport to apply it to human beings (G–21 at 3).) Neither the approved analytical method nor any other method known to me is capable of measuring DES at the 1 ppt level.

Dr. Gross' testimony suggests, but, read carefully, does not state, that his calculation accorded with the regulations published by FDA to describe the agency's requirements for analytical methods under the DES exception (see G–24). That regulation has been invalidated on procedural grounds, *Animal Health Institute* v. *FDA*, Civil No. 77–806 (D.D.C. Feb. 8, 1978) and reproposed in a somewhat modified form (44 FR 17070; March 20, 1979). I do not, in this Decision, rely on either the invalidated regulation or the proposal. It must be noted, however, that the 1 ppt calculation of Dr. Gross and Dr. Rodricks neither accords with the procedure set out in the regulation nor represents an appropriately conservative calculation of a "safe" level for DES (cf. Tr. at 1082).

As discussed in section II(A)(2), DES residues in meat can be expected to be made up not only of DES but also of various metabolites of that substance. The computation of a "safe" level of DES must therefore be based upon the results of animal testing not only of DES but also of the metabolites of DES that appear suspect (cf. G–72 at 10). If steers transform DES into a metabolite that is not produced when DES is fed to mice and that metabolite is more carcinogenic than DES itself, calculations from the Gass mouse data will provide a "safe" dose that is too high.

The criticisms of the Bureaus' witnesses' calculations of a 1 ppt "no residue" level for DES set out above show only that that calculation is not sufficiently conservative. Testing of DES metabolites might produce a lower "no residue" level for the totality of DES and its metabolites but would not produce a higher one.

The manufacturing parties, however, argue that the procedure utilized in calculating the 1 ppt figure is totally invalid from a completely different perspective. They rely on the testimony of their witness, Dr. Weaver, and upon various internal FDA memoranda to support their criticisms of the method of calculation used. They argue that that method is based upon unduly conservative assumptions and has not been shown to provide consistent results when the same data are utilized as a basis for calculation (Manufacturing Parties' Exceptions at 195–204). They also argue that the Bureaus' witnesses used the wrong data as a basis for their conclusion. They contend that a proper calculation would (1) be based upon all data in the Gass study, (2) ignore the 6.25 ppb result, and (3) incorporate results from the uncompleted NCTR study (discussed in section III(D)(2)(a) of this Decision) (id. at 204–06).

The FDA, as noted above, had issued a regulation that relied upon the method of calculation purported to have been used by Drs. Condon and Rodricks (but not by Dr. Gross (Tr. at 423) (G–24)). I decline to decide, on this record, whether the method utilized (the modified "Mantel-Bryan technique") is appropriate for use—or was applied correctly here—because, for the reasons stated above, I find 1 ppt calculation unusable in any event and I do not rely on it.

The decision not to rely upon the 1 ppt figure avails the manufacturing parties not at all, however. My criticism of the Bureaus' 1 ppt calculation applies with equal force to the manufacturing parties' alternative calculation; they, too, ignore the issue of DES metabolites. I am left, therefore, with the conclusion that no no-effect level or acceptable level of risk has been shown for DES. The record does not allow me to determine what level of DES might be low enough to cause less than one cancer in one million persons (assuming that that level may be equated to "no residue"). The record provides no basis for concluding that that level is not well below the 2 ppb that the manufacturing parties have claimed as the lowest level of measurement for the approved method.

My rejection of 2 ppb as an adequate lowest limit of measurement does not reflect any "never-ending search for more and more delicate methods of analysis" (see Manufacturing Parties' Exceptions at 28). Rather, it reflects a "rule of reason" (id.), which embodies the basic principle that a method of analysis should have a lowest limit of measurement that is low enough to protect the public from cancer caused by an animal drug. My dissatisfaction with the limit of 2 ppb is based on the evidence of record that DES is an animal carcinogen and the lack of information sufficient to show that DES and its metabolites, when present at the level just below 2 ppb, are safe or present an acceptable risk.

(iii) *Practicality.* The manufacturing parties argue that practicality is not an attribute necessary for approval of an analytical method for purposes of the DES exception to the Delaney Clause (Manufacturing Parties' Exceptions at 210). They base their argument on statements made by former FDA chief counsel Peter Hutt before a Congressional committee (id.). Contrary to the manufacturing parties' position, however, Mr. Hutt did not say that an approved method need not be sufficiently practical for regulatory purposes. Rather, he said that a method need not be approved to be used for regulatory purposes. Hearing before the Health Subcommittee of the Senate Labor and Public Welfare Comm. on S. 2818, 92d Cong., 2d Sess. 41 (1972). More importantly, as a matter of common sense, I can not find that no residues of a drug will be found in edible tissues of treated animals by an analytical method if that method is not practical enough to be used to analyze such tissues in the normal course of business.

The mouse uterine/paper chromatography method is not practical for regulatory purposes. As the record shows, it takes over 2 weeks to perform the assay (G–26 at 2–3; G–67 at 3; M–170 at 2). The meat of animals whose livers were examined would normally have moved to market in a 2-week period (G–26 at 3). One manufacturing parties' witness did testify on cross-examination that he performed the assay in 9 days (Tr. at 1846). The fact that one laboratory can perform the assay in 9 days does not mean that regulatory laboratories carrying on a variety of work can consistently perform it in that period. Moreover, even if the assay could be completed consistently within 9 days, that length of time would

constitute an unacceptable delay in the regulatory process.

The evidence also revealed that the mouse uterine/paper chromatography method is technically difficult to perform (G–67 at 3). A large number of mice are required (Tr. at 514), and their environment—including cages and feed—must be carefully controlled (G–67 at 3). Neither the quantity of animals nor the technical expertise necessary for use of this method are generally available in government regulatory monitoring laboratories (G–26 at 3). The United States Department of Agriculture has determined that the method is not practical for regulatory use (Tr. at 487). I reach the same conclusion.

(iv) *Specificity.* Specificity is one of the cardinal attributes of a regulatory method. The method should respond monotonically to (i.e., show a continuously increasing response to) increasing concentrations of the substance measured (DES) and that substance only. My analysis of the evidence on the issue reveals a problem. The Bureaus did not provide expert testimony that the approved method is not sufficiently specific. Indeed, one Bureau witness stated that the paper chromatography assay provides the requisite specificity to the approved method (G–72 at 10). Yet, there is no objective evidence in the record—or elsewhere, as far as I know—that the approved method is sufficiently specific.

I conclude that the approved methods are not adequately specific for use. I recognize that, because the Bureaus failed to advance this argument, it would be unfair to rely upon it as a basis for revoking the approved methods. There are, however, three other independent bases for my decision to revoke the approval of this method: (1) the fact that there has been no showing that this assay provides information about the levels in edible tissues of all of the metabolites of DES that potentially have a carcinogenic effect, (2) the failure of the method to measure DES residues at a level at which those residues are shown not to present a significant risk from cancer, and (3) the method's impracticability. For that reason, I reject the idea that I must either accept the consensus of testifying experts that the method is sufficiently specific or remand the issue for further consideration. I wish to make clear, however, that I do not rely on the following expression of my views on this subject as a basis for my rejection of the approved method.

The question that must be answered by an analytical method for DES is: "in this tissue, is there DES and, if so, how much?"

The first type of measurement of the approved method, i.e., measurement of uterotrophic effect in immature mice, can provide either one of two answers to this question:

> "There is no DES at levels at or above 2 ppb"; or alternately, "There are X DES equivalents (at or above 2 ppb) some of which *might* be DES."

(Measured residues are expressed as "DES equivalents" because the residue content of analyzed tissues is compared to known amounts of DES added to tissues fed to control mice.)

The record contains no information to show that an analyst finding X DES equivalents can say with some specific level of confidence, say 50 or 60 or 90, that no more (or less) than a fraction of those equivalents is indeed DES. Thus, the measurement of uterotrophic effects in immature mice is entirely nonspecific.

This is so even if it is *assumed* that increasing DES equivalents in the tissue will cause increasing responses, i.e., if monotonicity of response is assumed. It has not been demonstrated, however, that this method even produces a monotonic response. (It is conceivable and indeed, judging from the developers' description of this assay (G–68 at 811 and 812, Figure 3), likely that, at some level, an increase in DES could fail to increase uterine growth.)

Paper chromatography of tissue extracts was incorporated into the approved analytical method so that the analyst could ascertain what fraction, if any, of what might be DES is indeed DES. In general, chromatography of any kind is a non-specific method of analysis. This lack of specificity of chromatographic methods was alluded to by Dr. Abramson in his testimony (M–38) discussing gas liquid chromatography, one of the most specific chromatographic methods of today. Single run paper chromatography, one of the most primitive chromatographic methods, is less specific than gas chromatography. I can not agree that this assay is specific enough for the purposes at hand.

(b) *The Gas Chromatography/Mass Spectrometry Method.* The evidence that the gas chromatography and mass spectrometry assays when used together constitute a method that is accurate, dependable, and practical (M–38 at 15–18, M–128 at 8) is convincing and not seriously controverted by the Bureaus. Like the mouse uterine/paper chromatography method, however, the gas chromatography/mass spectrometry method is inadequate with respect to its lowest limit of reliable measurement and with respect to its specificity.

(i) *Lowest Limit of Reliable Measurement.* Expert testimony at trial firmly established that for regulatory purposes the lowest limit of reliable measurement is 2 ppb (M–38 at 17–18; M–93 at 2; M–128 at 8; M–164 at 1; Tr. at 1361). For the reasons discussed in detail in section II(A)(3)(a)(ii) above, that limit is not acceptable for approval of an analytical method for DES.

(ii) *Specificity.* Like the mouse uterine/paper chromatography method, the gas chromatography/mass spectrometry method is not adequately specific for regulatory purposes. The gas chromatography/mass spectrometry method upon which the expert testimony was based (known as the modified Donoho procedure) is described in M–39. This method provides for the selection of a single mass or ion for identification (M–39 at 521–22). Yet, as the manufacturing parties' Dr. Abramson testified, the identification of a single mass or ion does not allow definitive identification without a confirmatory step in which more than one ion must be monitored (M–38 at 13–14). Therefore, it appears that the method as described in M–39 is not sufficiently sensitive to determine identity reliably.

There is a direct relationship between the number of ions monitored and the lowest limit of reliable measurement in this method. Increasing the number of monitored ions yields a higher lowest limit of reliable measurement (see, e.g., M–38 at 19). Thus, achieving specificity with the gas chromatography/mass spectrometry method will yield a higher lowest limit of reliable measurement than the 2 ppb suggested by the experts.

(4) *Conclusion As to Analytical Methods.* For the foregoing reasons, I find that neither the approved method nor any other method is acceptable as an analytical method for DES for purposes of the DES exception to the Delaney Clause. As noted, by order issued today, I have revoked 21 CFR 556.190, the regulation approving the current analytical method for detection of residues of DES.

(B) Effect of Revoking Currently Approved Method for Testing Drug Residues in Edible Animal Tissues Without Implementation of Another Approved Method

An applicant for approval of an NADA for a carcinogenic drug must submit, as part of that NADA, an acceptable method of analysis to detect residues of the drug in edible products of the treated animal, 21 CFR 514.1(b)(7)(ii). The statutory provision describing the contents of an NADA is clear: it requires the submission of a

"description of practicable methods for determining the quantity, if any, of [the] drug in or on food, and any substance formed in or on food, because of its use * * *," 21 U.S.C. 360b(b)(7). In addition, as the legislative history of the DES exception (discussed below) shows, that provision contemplates that the applicant will have the responsibility for developing an analytical method for a carcinogenic drug. This has been the FDA's consistent interpretation of the new animal drug provision. (21 CFR 514.1(b)(7)(ii), promulgated on September 14, 1971 (36 FR 18375), was the first interpretation by regulation of the 1968 New Animal Drug Amendments.)

When an applicant for approval of an NADA for a carcinogen fails to submit an adequate analytical method to detect residues, it of course follows that no regulation setting out an approved analytical method will be promulgated for the applicant's drug. The agency then cannot find that no residue of the drug will be found by an approved method; the DES exception to the Delaney Clause can not be applied; the Delaney Clause does apply and the NADA may not be approved, 21 U.S.C. 360b(d)(1)(H).

If the Commissioner determines, based on new information together with previously available information, that the approved analtyical method for detecting residues of an animal drug is inadequate, it is his responsibility to revoke the regulation that sets out that method. 21 U.S.C. 360b(e)(1) then compels him to withdraw all NADA approvals that were based on compliance with that regulation because 21 U.S.C. 360b(d)(1)(H) (the Delaney Clause) becomes applicable to the drug.

The manufacturing parties argue that the DES exception remains in effect unless and until the FDA finds illegal residues, using an approved analytical method, in the edible tissues of animals. They contend that if there is no approved analytical method to measure residues, the Delaney Clause does not authorize withdrawal of NADA approvals, no matter how high the residue levels may be. The manufacturers claim support for their theory in the opinions in *Hess & Clark, supra,* and *Chemetron, supra,* the legislative history of 21 U.S.C. 360b(d)(1)(H), and statements made by FDA officials in 1972. In addition, they argue that withdrawal of approval of the DES NADA's due to revocation of the currently approved analytical method would constitute an administrative repeal of the DES exception and permit the Commissioner to expand the grounds for withdrawal of an approved NADA beyond those listed in 21 U.S.C. 360b(e)(1) (Manufacturing Parties' Exceptions at 27–32).

The manufacturing parties' reliance on the *Hess & Clark* and *Chemetron* opinions is misplaced. Neither opinion addresses the issue of the operation of 21 U.S.C. 360b(d)(1)(H) in the absence of regulations describing an approved method for determining whether drug residues exist inedible tissues. The court in *Chemetron* does state: "The 'DES' exception to the Delaney Clause, discussed above, continues effective unless the agency detects residues in a slaughtered animal while using an approved test method, "495 F.2d at 999. The context in which this statement is made, however, makes it clear that the court was not considering a situation in which no method was approved. Rather, the court was assumning the continued existence of an approved method.

The legislative history of the DES exception does not support the manufacturing parties' argument. The Delaney Clause was added to the Food Additives Amendment passed in 1958 (Pub. L. No. 85–929, 72 Stat. 1785). The Delaney Clause was then incorporated in the 1960 Color Additive Amendments (Pub. L. No. 86–618, 74 Stat. 399). The DES exception was first proposed during consideration of the Color Additive Amendments in 1960. See, e.g., H.R. Rept. No. 1761, 86th Cong., 2d Sess. 89 (1960). It finally was added to the Food additive and color additive provisions as part of the Drug Amendments of 1962 (Pub. L. No. 87–781, 76 Stat. 785). The 1968 New Animal Drugs Amendment (Pub. L. No. 90–399, 82 Stat. 343). consolidated the Food additive and new drug provisions that dealt with animal drugs and incorporated the Delaney Clause and DES exception from the food additive provision.

The legislative history does not contain any direct statements of how the Delaney Clause and DES exception should apply to a drug for which no analytical method is approved. That history does clearly support, however, two propositions, each of which is a basis for the agency's interpretation of the statute and its rejection of the manufacturing parties' contrary interpretation.

First, it is clear that the burden was placed upon the NADA applicant to develop an appropriate method of detection. In a letter submitted to the committee holding hearings on the DES exception as proposed in 1960, the Secretary of Health, Education and Welfare, stated:

> [I]t should be clearly understood that the industry still would have the responsibility of developing adequate analytical methods for detecting residues and furnishing them to the government with a petition for the approval of an additive.

(Cited in Hearings of FDA "Study of the Delaney Clause and Other Anticancer Clauses" Before a Subcommittee of the Committee on Appropriations, 93rd Cong., 2d Sess. 203–04 (1974).) The manufacturing parties have cited nothing in the legislative history of the DES exception that conflicts with the Secretary's expressed understanding of that exception.

Congressional inquiries into the DES exception since its passage have also supported the agency's view that an applicant must produce an acceptable analytical method. See, e.g., H.R. Rept. No. 93–708, 93rd Cong., 1st Sess. (1973), at 17, 26–27.

This allocation of burden is consistent with the general scheme of all the premarketing clearance provisions of the Food, Drug, and Cosmetic Act—those covering food additives (21 U.S.C 348, adopted in 1958), color additives (21 U.S.C 376, adopted in 1960), human drugs (21 U.S.C 355, adopted in 1938 and amended in 1962) and animal drugs (21 U.S.C 360b, adopted in 1968). Under all of these provisions Congress has consistently required that the manufacturer or other sponsor seeking approval of a substance or a product satisfy the burden or proving every element necessary for approval. See 21 U.S.C 348(b); 355b(b); 360(b); 376(b). The present case merely illustrates this fundamental and broadly applicable principle of public health protection deeply embedded in the Federal Food, Drug, and Cosmetic Act. There is no reason to treat the requirement for an adequate analytical method for residues caused by a carcinogenic animal drug any differently than the requirement that a food additive or color additive or human drug be shown to be safe. Thus, it is the manufacturing parties' responsibility to develop an acceptable method, and it follows logically that, if there is no acceptable method, Congress did not intend the manufacturing parties to benefit from that fact.

Second, the legislative history illustrates Congress' understanding that the Delaney Clause would apply unless the Commissioner could make a finding that no residues will be found in the products of the treated animal. In responding to the argument that the DES exception would diminish the Delaney Clause's protection of the public health, Congressman Harris stated (108 Cong. Rec. 21081 (1962)):

This amendment places the resonsibility on the Secretary of Health, Education and Welfare *to make a positive finding* that under the conditions of use and feeding specified in the proposed labeling and reasonably certain to be followed in practice, the feed additive will not, first, affect the animal; and, second, *that no residue of the additive will be found* in any edible portion of the animal after slaughter (emphasis added).

As the manufacturing parties point out, Congressman Harris had earlier been assured that the DES exception provided "the authority for the Secretary to see that no residue of the additive shall be found" (id. at 21080).

Senator Kefauver, a sponsor of the Drug Amendments in the Senate, explained the DES exception as follows (108 Cong. Rec. 20869 (Oct. 3, 1962)):

The provision stipulates that the anti-cancer proviso of existing law shall not apply with respect to the use of a substance—for example, a veterinary drug— as an ingredient of feed for animals which are raised for food production if the *Secretary finds * * * that no residue of the additive will be found* after slaughter or in any food product of the living animal—such as milk or eggs (emphasis added).

Senator Humphrey, also a strong supporter of the Drug Amendments (108 Cong. Rec. 22053 (1962)), described the DES exception and then stated that it

preserv[es] in its full vigor the Consumer protection now afforded by [the Delaney Clause].

I reiterate—consumer protection is assured.

These quotations (particularly the first two) reinforce the conclusion that is already clear from the language of the statute: the operations of the DES exception depends on the Commissioner making a finding of no residue (by use of a method approved by regulation). The DES exception does not begin to operate without that prerequisite finding. Clearly excluded by the language and the legislative history is the manufacturing parties' interpretation that the exception can apply without the prerequisite finding and that the discovery of some residue is necessary to prevent or stop its operation. That interpretation is totally inconsistent with the explanations offered by Rep. Harris and Senator Kefauver and it certainly would not preserve consumer protection "in its full vigor" as stated by Senator Humphrey. Indeed, under the manufacturing parties' interpretation, any deficiencies in analytical methodology that prevented identification of residues in the range material to protection of public health would be at the expense of public health protection. That certainly is not what Congress intended.

The congressional understanding that the Secretary (or, by delegation, the Commissioner) could find that "no residues" would be found in edible tissues may have been based on an operational definition of the term "no residue" as equivalent to no residues above a level that can be considered virtually safe. FDA has interpreteed the DES Exception in this way (see, e.g., 44 FR 17070 (March 20, 1979); G–24). Another conceivable explanation, which I consider improbable, is that the Congress was less scientifically sophisticated and believed that it was possible for the Commissioner to find that absolutely no residues would exist in the edible tissues of treated animals.

In any case, there was, without question, a congressional concern that the Commissioner find that there are "no residues" in edible tissues and there was a belief on the part of the legislators that the DES exception did nothing to diminish the protection to the public health afforded by the Delaney Clause. It is hardly consistent with that congressional intent to urge that Congress meant the Delaney Clause to be inapplicable whenever no analytical method had been approved for a drug.

The manufacturing parties rely upon a statement by former FDA chief counsel Peter Hutt at a 1972 Congressional hearing. In the statment referred to, he defended the proposition that the Delaney Clause did not sanction withdrawal of approval of NADA's based on the finding of residues by unapproved methods, hearings on Regulation of Diethylstilbestrol Before the Intergovernmental Subcommittee of the House Government Operations Committee, 92d Cong., 2d Sess. 385 (1972). Mr. Hutt advocated his position forcefully and extemporaneously (at one point informing the Committee that Congress did not appreciate what it was doing in passing the DES exception (id. at 386)). His statements cannot fairly be taken out of context to bear upon a question—whether the Delaney Clause applies if there is no approved method for a drug—entirely different from the issue he was addressing.

To the extent that Mr. Hutt's comments may be read to suggest that the Clause does not apply when no method exists, I explicitly disavow them on behalf of the FDA. Such a reading would be inconsistent with the language, legislative history, and purpose of the statute and with the FDA policy that supports the proposed regulations setting requirements for analytical methods (44 FR 17070 (March 20, 1979), cf. G–24).

The maunfacturing parties also refer to a statement included in material forwarded by FDA to Senator Proxmire in 1972 (M–167 at 4191–92). This statement, that the Delaney Clause requires findings by the approved method, assumed, as did Mr. Hutt's statements, that an approved analytical method existed for the drug in question (there DES). That statement did not address the question of the applicability of that clause when there is no approved method.

The manufacturing parties' argument that withdrawal of an NADA on the basis of revocation of the methods regulation is an administrative repeal of the DES exception is without merit. As Commissioner, I may not, of course, simply ignore the DES exception to the Delaney Clause, nor may I act arbitrarily and capriciously when a method is submitted for approval. I must approve an analytical method if an appropriate one is presented. On the other hand, it is implicit in the statutory requirement that the Commissioner "prescribe or approve" the methods of analysis that he must evaluate the method submitted and refuse approval of that method if he finds it inadequate. In sum the withdrawal of approval of an NADA upon revocation of the analytical method upon which approval is based implements, rather than subverts, the statute, including the DES exception.

(c) *Conclusions As to Delaney Clause Issue.* For the reasons discussed in this section II, I find that (1) approved analytical method for detecting DES residues is inadequate and that (2) no alternative method is adequate for use as an analytical method to detect DES residues. I reject the manufacturing parties' argument that the DES exception to the Delaney Clause is applicable if there is no approved analytical method for DES residues. I conclude, therefore, that the revocation of 21 CFR 556.190 requires the withdrawal of approval of the DES NADA's pursuant to 21 U.S.C. 360b(e)(1)(B) and 360b(d)(1)(H).

III. The Safety Clause

(a) Burden of Proof

for purposes of convenience, I refer to that part of 21 U.S.C. 360b(e)(1)(B) that does not deal with the Delaney Clause as the "safety clause." The burden of proof in this proceeding on the safety clause issue is derived from the clause itself, which is as follows (21 U.S.C. 360b):

(e)(1) The [Commissioner] shall, after due notice and opportunity for hearing to the applicant, issue an order withdrawing approval of an application filed pursuant to subsection (b) of this section with respect to any new animal drug if the [Commissioner]

finds * * * (b) that *new evidence* not contained in such application or not available to the [Commissioner] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, *evaluated together with the evidence available to the [Commissioner] when the application was approved, shows that such drug is not shown to be safe* for use under the conditions of use upon the basis of which the application was approved * * * (Emphasis added).

As is apparent from the italicized language, approval may be withdrawn pursuant to the "safety clause" if new evidence, evaluated together with previously existing evidence, shows the drug is not shown to be safe. As Congress was careful to make clear, "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 Bureaus rely. DES was first approved in 1954. The Gass study was published in 1964, and did not come to the attention of FDA until 1971 (see M–1). The evidence concerning DES residues was not available until the 1970's.

Because the Bureaus are the proponents of withdrawal, it is appropriate that they have the burden of proving that the first "showing" (i.e., a showing that the drug is no longer shown to be safe) has been made, see *Hess & Clark, Division of Rhodia, Inc.*, v. *FDA*, *supra*, 495 F. 2d at 992. The Bureaus did not dispute this point.

The controversy arises over what is sufficient to constitute the required showing. The manufacturing parties argue that the Bureaus' burden is, in effect, to show that use of the drug is unsafe. There is, however, a clear congressionally recognized difference between "unsafe" and "not shown to be safe." Indeed, the statute uses both terms and clearly distinguishes between them. Compare 21 U.S.C. 360b(e)(1)(A) with 21 U.S.C. 360b(e)(1)(B). The former paragraph requires a finding that a drug is "unsafe"; the latter, a finding that the drug is "not shown to be safe." If the two terms were the same, there would not be two subparagraphs.

The Court of Appeals in *Hess & Clark, Division of Rhodia, Inc.*, v. *FDA*, *supra*, 495 F. 2d at 993, focusing on the residue issue (discussed below in sections III (B) and (C) of this Decision), stated its view of the burden question:

> We think it implicit in the statute that when the FDA proposes to withdraw an approval because new evidence shows the drug leaves residues, it 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. This is at least the case where, as here, the residues are of unknown composition. (Emphasis added.)

It is, of course, not possible to write a formula, semantic or otherwise, that will tell the decisionmaker exactly how much evidence is required to show that a drug is no longer shown to be safe. The Administrative Law Judge's formulation is as good as any: "In other words, the Bureaus 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" (I.D. at 8). I adopt this statement of the burden of proof in this proceeding. Even if the Bureaus had the burden to show that the presently approved uses of DES were unsafe, however, I would have to find, on this record, that they have carried that burden.

(B) Evidence That DES Use Results in Residues in Edible Tissues

I have carefully considered whether the evidence in the record shows that use of DES as an animal drug results in DES residues in edible tissues. (Except where the context indicates otherwise, a reference to "DES residues" in this Decision refers to residues identifiable as DES and/or its conjugates.) I have found convincing evidence on this issue from two separate sets of data: the radiotracer studies discussed in subsection (2) below and the results of the Department of Agriculture manufacturing program discussed in subsection (3). Though each supports the other, I find that each of these sets of data provides an independent basis for the conclusion that animal drug use under each of the approved DES NADA's does result in residues of DES and/or its conjugates in the edible tissues of treated cattle. I rely solely upon the radiotracer studies for my conclusion that approved uses of DES result in DES residues in the edible tissues of sheep. (As is discussed in detail in section III(D) below, I also find that these resulting residues are harmful.)

The residues in the tissues of treated animals observed by both the radiotracer studies and the Department of Agriculture monitoring program are not surprising. Anything administered to an animal's system remains in that system in small amounts indefinitely (see, e.g., M–167 at 4191; G–2 at 1192). The amounts of those residues, however, generally decrease as the time following administration increases. (One can visualize this phenomenon as an asymptotic or "decay" curve (see G–24 at 10428).)

When the withdrawal period for oral DES was originally set at 7 days, that action was not based upon the belief that after 7 days no DES residues would exist in meat (see G–72 at 3). Rather, that withdrawal period was set because at that point on the curve almost all residues would be below 2 ppb, which was once thought to be the safe dose for DES. It would be expected that the 7-day withdrawal period would result in residues in the 0.5 to 2 ppb range. Even a 14-day withdrawal period would reasonably be expected to result in residues at some level. What is said about the withdrawal periods for DES in feed is equally applicable to the required period between implantation of DES implants and slaughter of cattle with implants.

(1) *The Withdrawal Period.* A withdrawal period is the period before slaughter during which the animal feeder may not administer an animal drug. The withdrawal period allows the animal's body to dispose of some of the drug in its system. The approved withdrawal period for DES for both cattle and sheep feed is 7 days, 21 CFR 558.225. In 1974, FDA urged manufacturers to label their products for a 14-day withdrawal period (39 FR 11323; March 27, 1974). The agency has, however, taken the position that it will not approve supplemental NADA's to change the withdrawal date until the safety problems with respect to DES have been resolved; hence the continuation of the official 7-day withdrawal period in FDA regulations. Some manufacturers have apparently relabeled their drug for 14-day withdrawal (without objection from FDA), and others have not (Manufacturers' Exceptions at 46 n.*). Meanwhile, the Department of Agriculture has issued regulations requiring certification that DES was withdrawn from feed at least 14 days, before slaughter (9 CFR 309.16).

The manufacturing parties argue that, because 14-day periods are actually used, their NADA's should be evaluated on the basis of those periods. the statute is clear, however, that in deciding whether approval of an NADA should be withdrawn, the Commissioner is to consider whether new evidence shows that the drug is not shown to be safe for use "under the conditions of use upon the basis of which the application was approved," 21 U.S.C. 360b(e)(1)(B).

Should the manufacturing parties wish to seek approval of DES in feed under different conditions of use, they are free to do so. They must carry, however, the

burden of proving that the proposed new conditions of use are safe.

In order to provide as complete an analysis of the record as possible, however, I have made findings with respect to not only the 7-day withdrawal period but also the 14-day period. The latter findings assume, for purposes of argument, that the 14-day period is the approved withdrawal period.

(2) *Radiotracer Studies.* Several radiotracer studies were performed by scientists of the Department of Agriculture to determine the fate of DES in cattle and sheep. The results showed that very small amounts of DES remain in a number of different tissues of the animals treated with the drug.

In radiotracer studies, the scientist substitutes radioactive carbon (^{14}C) atoms for some of the non-radioactive carbon 12 atoms in the DES molecule. The molecule thus formed is biologically identical to the normal DES molecule except that it is now radioactive. The radioactivity allows the scientist to establish the absorption, distribution and excretory patterns of the compound of interest or its metabolites in biological systems, in this case, food-producing animals (G–76 at 3).

(a) *Oral Dosages in Cattle.*—(i) Studies. The currently approved conditions of use for DES in cattle feed permit up to 20 mg per head per day, with a withdrawal period of 7 days, 21 CFR 558.225. As discussed above, some manufacturers have labeled their products for a 14-day withdrawal period.

Two studies were done with cattle fed DES. The first, by Aschbacher and Thacker (G–2), involved the feeding to steers of a single oral dost of 10 mg ^{14}C-DES after the steers had been fed 20 mg per head of DES daily for 14 days. Because residues are observed in this type of study by detecting radiation in the tissues of treated animals (G–76 at 3), any radiation found would be attributable to the 10 mg of ^{14}C-DES. Cattle may be fed for up to 135 days (Tr. at 2023). Thus, total consumption of DES by a steer may amount to 2700 mg (20 mg × 135 days), or 270 times the amount of ^{14}C-DES administered in this study.

In this study, two animals each were sacrificed at 1, 2, 3, 5, 7, and 10 days after the ^{14}C-DES feeding. Dr. Aschbacher testified that radioactivity was observed in all sections of the gastrointestinal tract and in liver, kidney and bile-gall baldder in the animals sacrificed after 1, 2, 3, 5, and 7 days (G–1 at 3). The report of this test shows that some radioactivity was also observed in tissues of the steers sacrificed 10 days after the one-time ^{14}C-DES feeding (G–2).

The report of this study states the concentrations of radioactive material (above background) in the various tissues in the ppb equivalents of DES, on the assumption that all radioactive material is radioactive DES (G–2 at 1190, Table 4). The 7-day steers had, in their livers, 0.13 and 0.37 ppb. Standard deviations were listed as 0.04 and 0.07 for the first and second steers, respectively. After 10 days, 0.08 ppb (with a 0.04 standard deviation) was calculated for the livers of each of the two steers sacrificed. Therefore, the radioactive residues attributable to DES were found in livers of steers after more than the approved withdrawal period. The evidence from this study supports a finding that normal feeding of DES, even with a 7-day withdrawal period, results in DES residues in the animals' livers. This finding also applies by extrapolation to a 14-day withdrawal period. As discussed in the second paragraph of section III(B), tha amount of DES present after 7 days would decline but not disappear during the following 7 days.

It is true that the amounts of radioactivity found were small. The amounts of radioactive DES administered to the test animals also were small, however, compared to the amounts that are administered under the approved conditions of use.

The report notes that radioactivity was detected in the muscle of the steers sacrificed 24 hours, 5 days and 10 days after dosage, but not in the muscle tissues of other treated steers (id.). The manufacturing parties' Dr. Tennent stated his opinion that because of possible cross-contamination it is not possible to base any conclusions on the radioactivity found in muscle tissues (M–132 at 19). The Bureaus' Dr. Aschbacher also stated his opinion that no conclusions could be based upon the radioactivity found *in muscle tissues* of animals *sacrificed 5 and 10 days after dosing* (Tr. at 604). The published report of the study stated that ^{14}C-contamination did not appear to be an important factor in the liver, kidney, and bile-gall bladder samples when levels were above 0.1 ppb DES equivalents (G–2 at 1191).

In a 1975 report of his study to the Department of Agriculture, Dr. Aschbacher had also stated that, because of the low levels of radioactivity observed in muscle and the apparent randomness with which that radioactivity was seen there, he thought it was not possible to discount cross-contamination as the source of the radioactivity observed in muscle and carcass in the animals slaughtered after more than 24 hours (M–134 at 00097). With respect to the finding 24 hours after dosage, Dr. Aschbacher stated that the radioactivity observed in the muscle tissue was the result of the ^{14}C-DES dosage administered (id.). (He also noted that the fact that this residue was not analyzed meant that he could not conclude that DES was present. As discussed elsewhere, however, his analysis of other residues attributable to ^{14}C-DES showed that they contained DES and/or its conjugates, and I conclude therefore that this residue also contained DES or its conjugates.)

I do not rely upon the findings in muscle tissue in the animals sacrificed 5 and 10 days after dosage. I do, however, find that, as the researchers concluded (see M–134 at 00097), the radioactivity observed in the steers sacrificed 24 hours after dosage was a valid observation.

An isotope dilution procedure was used to characterize the radioactive material in liver tissues from two steers slaughtered after 2 days and one steer slaughtered after 7 days. Twenty-two percent of the radioactivity was confirmed as ^{14}C-DES in the 7-day steer, and 36 and 46 percent were so confirmed, respectively, in the 2-day steers (G–2 at 1190–91). Thus, I find that at least a part of the residues found in liver in this study is either free DES or a conjugate that hydrolyzes to free DES. As a scientific matter, this finding is also applicable to the radioactivity detected in muscle 24 hours after dosage. Therefore, I find the feeding of DES to cattle in this study resulted in residues of DES or its conjugates in muscle as well as in liver. See discussion of the conjugates issue below (section III(C) of this Decision).

A second radiotracer study with cattle was performed by Dr. Rumsey, et al. (G–79). In this study, 7 heifers and 8 steers were administered 3 daily radioactive doses of 1.68 mg ^{14}C-DES after having been pretreated with 10 mg daily doses of unlabeled DES for at least 60 days. One heifer and one steer each were then slaughtered after respective withdrawal times of 0.75, 1.5, 3, 5, 7, 9, and 14 days. One steer was slaughtered 30 days after withdrawal. Radioactivity above the background rate (which indicates residues traceable to the ^{14}C-DES dosages) was found in all parts of the liver of the 7-day steer and in two of five parts examined from the 7-day heifer. Thus, this study provides evidence that doses of DES that, combined, represent a level one quarter the size (i.e., 5 mg v. 20 mg) of the daily dose approved for use, result in ^{14}C-DES residues in liver when the approved withdrawal period is

observed. Radioactivity calculated to be at or above the level of 0.2 ppb DES equivalents in wet tissues was found in the muscle tissues of steers sacrificed 0.75 and 1.5 days after dosing (see discussion of the significance of findings in muscle tissues in the conclusion of this section below).

Some of the liver tissues from the test animals were taken by the Bureaus to Dr. Kenneth Williams of the Worcester Foundation for Experimental Biology for further analysis. He subjected the samples to reverse isotope dilution procedures to determine the identity of the radioactive material in the livers. Dr. Williams reported that all of the samples tested, some of which were of livers of animals that had been slaughtered 7 days after dosage, contained DES and/or its conjugates (G–99 at 3). Dr. Williams, by further testing, confirmed that the DES he had discovered was not pseudo-DES (see discussion in section III(B)(2)(e) (G–99 at 5).

According to Dr. Rumsey, Dr. Williams' test showed the presence of 0.03 ppb of DES equivalents in the livers of the animals sacrificed 7 days after last feeding (G–76 at 4). Dr. Rumsey stated the results of the isotope dilution studies cautiously, saying that those results "suggested the possibility of but did not prove to me" the presence of DES in the livers (id. at 3). Dr. Williams, on the other hand, was unequivocal in his statement that DES and/or its conjugates had been found in the livers he tested (G–99 at 3). I accept Dr. Williams' evaluation of his own results in these tests.

(ii) *Conclusion As to Oral Dosage in Cattle.* The fact that radioactivity was found in some tissues of treated animals and not in others could be because (1) the study was not sufficiently sensitive to detect all DES residues in each tissue analyzed or (2) DES residues did not exist in the tissues in which radioactivity above background was not detected. Because DES was found in all tissues (including muscle) in the animals with the shortest withdrawal dates, and no viable theory has been proffered to explain why all DES would disappear totally from some but not other tissues, I accept the former explanation. I therefore find that these radiotracer studies establish that when DES is fed to cattle, it leaves residues of DES and/or its conjugates in the edible tissue (including liver and muscle) of treated cattle.

One ^{14}C-DES feeding test used a radioactive dose of 10 mg. The other used, in three doses, approximately 5 mg of radioactive DES. Resulting radioactive residues detected were small, but such residues were detected. It is fair to infer from these results, in the absence of evidence to the contrary, that had the ^{14}C-DES been fed at 20 mg daily for 135 days, the residues observed would have been larger. On the other hand, it is also fair to assume that a 14-day withdrawal period would have led to smaller residues. I find that, on balance, the studies' results show that DES feeding of cattle under approved conditions of use leaves residues in edible tissues (including liver and muscle), whether a 7 day or 14 day withdrawal period is observed.

(b) *Implants in Cattle.*—(i) *Studies.* The approved conditions of use for DES implants in cattle allow implantation of two 15 mg-pellets per animal or, alternatively, three 12 mg-pellets per animal "at the start of the feeding period or approximately 120 days before marketing," 21 CFR 522.640(d) (2) and (3). Two studies were done with steers implanted with DES pellets.

The first, performed by Dr. Aschbacher, et al., involved the implantation of four steers with 28 mg of radio-labeled DES. The steers were killed at intervals of 30, 60, 90, and 120 days after implantation (G–5 at 530). A control group was made up of four steers implanted with DES pellets not containing radioactivity. These steers were slaughtered on the 28th, 58th, 88th, and 118th days after implantation (id. at 531). The tissues from the control animals were used to establish a background rate for radioactivity.

Radioactivity above the background rate (and thus traceable to the ^{14}C-DES implant) was observed in all tissues from treated animals examined, including muscle, liver, kidney, adrenals, heart, etc., with the exception of the visceral fat of one of the 90-day animals (G–1 at 4; G–5 at 535, Table 2). The radioactivity in the livers was further characterized by isotopic dilution procedures and determined to be, in part, either free DES or a hydrolysable conjugate of DES (G–1 at 5; G–5 at 535). The report states that the amount characterized as ^{14}C-DES in the livers was equivalent to 0.07 to 0.13 ppb of DES (G–5 at 535). (These figures were apparently derived from a calculation based on the ^{14}C activity observed in the tissues and the specific activity of ^{14}C-DES.)

Part of one of the two ^{14}C-DES pellets in the animal slaughtered after 120 days had not dissolved and was retrievable at the time of slaughter (G–5 at 534; G–1 at 4). Thus, presumably, the implant was still delivering DES to the system at the time of slaughter.

A second study on cattle with implants was performed by Dr. Rumsey, et al., (G–77). This study involved the implantation of ^{14}C-DES pellets into eight steers. Two implanted steers and one control animal were slaughtered respectively at 30, 60, 90, and 120 days after implantation. All but one of the treated steers sacrificed received two implants totaling 32.2 mg ^{14}C-DES. One of the two steers slaughtered after 120 days, which was of a lighter weight, received only one implant of 15 mg (G–77 at 551, 554, Table 1).

The steers slaughtered after 120 days showed radioactivity significantly (p less than 0.05) above background in tongue, spleen, adrenals, lung, kidney, bile, and liver (G–76 at 5). One of the steers showed radioactivity significantly above background in cheek muscle (id.). Radioactivity above background was not found in shoulder or rib muscle or in the brisket (id.).

As in the feeding studies discussed above, the lack of a finding of radioactivity in some tissues in this study may be the result of either (1) the relative insensitivity of the tests or (2) the fact that no residues actually exist in these tissues. Acceptance of the former explanation is the conservative approach and is also supported by the findings in the Aschbacher implantation study. Therefore, I adopt it. Thus, although Dr. Rumsey's results may be taken as evidence that DES residues in the shoulder or rib muscle and brisket tissues are not found at as high levels as those found in other edible tissues (e.g., tongue, kidneys, livers), they do not show that no residues would, in fact, occur in shoulder or rib muscle and brisket.

In this study, like the Aschbacher implant study, part of the implant still remained in the steers 120 days after implantation (G–76 at 6; G–77 at 559).

Livers from this study were provided to Dr. Williams for characterization of the radioactivity observed. All of the livers were found to contain DES or its conjugates, including livers from animals slaughtered 120 days after implantation (G–99 at 3; cf. G–76 at 6). For the reasons stated in my discussion of Dr. Williams' analysis of livers from the feeding studies, his findings here with respect to livers apply also to other tissues.

(ii) *Conclusions As to Implant Studies in Cattle.* For the reasons discussed with respect to the feeding studies, I attribute the variations in the findings of radioactivity in the implant studies to inherent limitations in the levels of detection of the methods utilized.

As noted, approved conditions of use allow 30 to 36 mg implants inserted 120 days before slaughter. Since residues were observed (in the Aschbacher study