

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

ENCLOSURE 1

SUBJECT: EPA - FDA Meeting Held on January 7, 1976

DATE: 12 JAN 1976

FROM: Alan Levin *Alan Levin*
Special Assistant for Water Supply & Pesticides

TO: Memorandum of Record

Participants

FDA

Sam D. Fine
Sherwin Gardner
Terry Coleman
Robert Angelotti
Howard R. Roberts
Robert M. Schaffner
Bob Lake
Gerard L. McCowin
Richard J. Ronk
John R. Wessel

Associate Comm. for Compliance
Deputy Commissioner
Associate Chief Counsel for Food
Associate Dir. Compliance, Bur. Foods
Acting Director, Bureau of Foods
Assoc. Director for Technology, Bur. Foods
Reg. Coord. Staff Bureau of Foods
Division of Food and Color Additives
Director, Div. of Food and Color Additives
Scientific Coordinator, Office of
the Associate Commissioner for Compliance

EPA

William M. Upholt
Alan Levin
Andrew Breidenbach
Christopher Little
Victor J. Kimm

Senior Science Advisor, Office of Water
and Hazardous Materials
Special Assistant for Water Supply and
Pesticides
Assistant Administrator for Water and
Hazardous Materials
Assistant General Counsel
Deputy Assistant Administrator for
Water Supply

1. The purpose of the meeting was a get acquainted session for Commissioner Schmidt and Dr. Breidenbach and to explore areas of mutual interest to our two agencies. Commissioner Schmidt was unable to attend and Deputy Commissioner Gardner substituted for him.
2. Dr. Breidenbach made an opening statement indicating a number of areas where EPA and FDA regulatory responsibilities may overlap. Among these are:

- a. Pesticides that may contaminate food or feed.
- b. Pesticides which may also be drugs.
- c. Toxic Substances
- d. Domestic Water Supplies.

Dr. Breidenbach pointed out that relations between our two agencies have generally been good and have resulted in a number of interagency agreements, particularly in the area of pesticides. He indicated that he preferred to limit the discussion at this meeting to water supply.

- 3. Deputy Commissioner Gardner responded that he endorses the idea of an interagency agreement on water supply matters.
- 4. Mr. Kimm outlined the principal problems involving drinking water as they relate to FDA:
 - a. Enforcement of interstate carrier watering points;
 - b. Regulation by product or food additives (such as pipe);
 - c. Water supplies not covered by the Safe Drinking Water Act;
 - d. Bottled water
- 5. It was agreed that Mr. Kimm and Dr. Angelotti would take the lead to form a task force consisting of representatives of EPA and FDA to identify issues requiring top level decision in the area of water supply, with item 4b. above receiving the highest priority.
- 6. Additional task forces on other problems such as pesticides and toxic substances would be formed as needed.
- 7. There was mention made of the need for further consultation on regulatory philosophies. EPA indicated their increasing use of risk/benefit evaluation as a basis for regulation and expressed a need for a degree of understanding, if not agreement, between the regulatory agencies, especially FDA and EPA but eventually probably OSHA and CPSC as well. FDA indicated a willingness to discuss it further at a later date.

cc: Participants

January 7, 1976

MEMORANDUM OF CONFERENCE

ENCLOSURE 2

Present : EPA Participants:

Dr. Andrew W. Breidenbach, Assistant Administrator for
Water and Hazardous Materials
Dr. William M. Upholt, Senior Science Advisor, Office of
Water and Hazardous Materials
Alan Levin, Special Assistant for Water Supply and Pesticides
Christopher Little, Assistant General Counsel
Victor J. Kimm, Deputy Asst. Administrator for Water Supply

FDA Participants:

Sherwin Gardner, Deputy Commissioner
Sam D. Fine, Associate Commissioner for Compliance
John R. Wessel, Scientific Coordinator, Office of the
Associate Commissioner for Compliance
Terry Coleman, Associate Chief Counsel for Food
Dr. Robert Angelotti, Associate Director for Compliance,
Bureau of Foods
Dr. Howard R. Roberts, Acting Director, Bureau of Foods
Dr. Robert M. Schaffner, Associate Director for Technology,
Bureau of Foods
Bob Lake, Regulations Coordination Staff, Bureau of Foods
Richard J. Ronk, Director, Division of Food and Color
Additives, Bureau of Foods
Gerad L. McCowin, Division of Food and Color Additives,
Bureau of Foods

Dr. Breidenbach and his associates met with Deputy Commissioner Sherwin Gardner and members of the staff of the Food and Drug Administration in the Commissioner's Conference Room in FB-8 on January 7, 1976, as a follow-up to Dr. Breidenbach's letter of November 7, 1975, to Dr. Alexander M. Schmidt, Commissioner of Food and Drugs.

Dr. Breidenbach explained that he had just recently been appointed Assistant Administrator for Water and Hazardous Materials, and that he realized there were several areas of concern which require a close working relationship between EPA and FDA. He listed the following areas:

1. Water Supply - Interstate Carrier Program
2. Pesticides
 - a. Contamination of food and animal feed - setting of tolerances and action levels.
 - b. Pesticides as drugs for both man and other animals.

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3. Toxic Substances

Dr. Breidenbach referred to the current problem with PCB's and the new legislation now in the Congress on toxic substances. He said he was aware of the cooperation there has been in the past between Glen Sweitzer, Coordinator, Office of Toxic Substances, EPA and Mr. Wessel on problems dealing with toxic substances.

4. Philosophy of regulation

Dr. Breidenbach made reference to the generation of data on which regulations are based. He also called attention to EPA's publication in the Federal Register of December 24, 1975, under the new Safe Drinking Water Act, of National Interim Primary Drinking Water Regulations. He stated that Mr. Train was sending to FDA through Secretary Mathews an official communication on the work required by FDA on bottled drinking water as a result of the new EPA regulations. (Later during the meeting Dr. Upholt said that he meant, under term "philosophy of regulation," the kind of philosophy FDA follows due to the Delaney Clause of the Food Additives Amendment).

5. NCTR

Dr. Breidenbach referred to the cooperative program of the two agencies at Pine Bluff, Arkansas.

It was Dr. Breidenbach's view that the main concern at the moment for both agencies is the problem of water supply. He asked Victor Kimm to discuss the interface between the two agencies on this problem.

Mr. Kimm referred to the interchange of information required because of overlapping jurisdiction under the various laws administered by the two agencies. He noted the difficult judgments required on the problem of contaminants, such as chloroform in the water supply of New Orleans, Louisiana. He pointed out the impact of FDA's publication of its proposed regulation on PVC, which included the problem of migration of vinyl chloride from PVC pipe to water. The need for the public and the regulated industries to know who does what on the Interstate Carrier Program was emphasized by Mr. Kimm. He also referred to what he identified as "products problems."

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At Mr. Gardner's request, Dr. Angelotti reviewed for the EPA visitors FDA's concerns with water problems under both the Food, Drug and Cosmetic Act and the Public Health Service Act. Reference was made to the problems that arise when EPA applies the term "Use Prohibited" to water supplies, when there are administrative deficiencies or there is no standard. It was pointed out that in some instances where EPA has applied this designation, FDA has made a determination that the water is safe, and thus FDA allows it to go on interstate carriers, and further allows it to be used for manufacturing foods. Reference was made to the meeting held by Messrs. Fine, Angelotti, Naciewicz and McNamara with Mr. Kimm and other EPA staff members in June of 1975, where there was a discussion of the new authority granted to EPA under the Safe Drinking Water Act on control of water on interstate carriers. It was pointed out that under the old Public Health Service, where FDA had not been involved, there had been no concern with food additives in water (Mr. Kimm's "products problems"). The problem with PVC caused FDA to look at vinyl chloride migration to water; this logically could lead to FDA looking at liners for reservoirs, etc.

After Dr. Angelotti's review there was a general discussion, with a consensus being reached that there should be additional formal agreements between the two agencies to deal with problems caused by overlapping jurisdiction. It was agreed that the problems in the pesticide area would be handled by Mr. Wessel with the current EPA staff members that he has been working with. Mr. Wessel gave a brief review of the status of the agreements with EPA on pesticides. It was agreed that a task force would be set up, headed by Dr. Angelotti and Mr. Kimm, to deal with the water supply -- interstate carrier problems. It was agreed that at intervals of 2 to 4 months on an as-needed-basis, Dr. Breidenbach would telephone Mr. Fine to arrange for discussions at the Commissioner/Assistant Administrator level.


Sam D. Fine

cc: HF-1 HF-2 HFC-1 HFC-2 HFC-13(Wessel) GCF-1 GCF-1(Coleman)
HFF-300 HFF-1 HFF-400 HFF-302 HFF-330 HFF-330(McCowin)

SDFine:br:eh 1/9/76

SPI-25986

**DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE**

Food and Drug Administration

[Docket No. 75F-0308]

MONSANTO CO.

Filing of Petition for Food Additive

Correction

In FR Doc. 75-30109, appearing at page 82427, in the issue for Monday, November 10, 1975, change the seventh line of the second paragraph to read as follows: "sidered in a draft environmental impact".

[Docket No. 76N-0002]

ELANCO PRODUCTS CO. ET AL

Diethylstilbestrol; Notice of Opportunity for Hearing on Proposal to Withdraw Approval of New Animal Drug Applications

The Food and Drug Administration (FDA) is proposing to withdraw approval of all outstanding new animal drug applications for use of diethylstilbestrol in animals used for food for human consumption on the ground that use of the drug results in residues that have not been shown to be safe within the meaning of the act and that render continued approval of the drug unlawful under the Delaney anticancer clause of the Federal Food, Drug, and Cosmetic Act. Holders of approved applications have until February 11, 1976 to submit requests for hearing in accordance with § 514.200 (21 CFR 514.200). Such requests should be identified with the Hearing Clerk docket number found in brackets in the heading of this notice.

BACKGROUND

Diethylstilbestrol (DES), a synthetic estrogen used by feeders of cattle and sheep as a growth promotant, has been shown to cause a statistically significant increase of cancer in female C₃H mice at the lowest levels at which it was tested, i.e., 6.25 parts per billion (ppb). In humans, a statistically significant relationship has been identified between the administration of DES to pregnant women and the appearance in daughters born of these pregnancies of a rare type of cancer—adenocarcinoma of the vagina.

Since 1938, any new drug for use in animals, just as any new drug for human use, has been required to be shown to be safe for its intended uses. Even before the enactment of the Food Additives Amendment of 1958 (sec. 409, Pub. L. 85-929, September 6, 1958, 72 Stat. 1785-1788 (21 U.S.C. 348)), FDA had interpreted this basic safety requirement as demanding proof that drugs intended for use in animals used for human food would not cause harm if ingested by humans.

DES was first approved for use in cattle feed in November 1954. A new drug application (NDA) for the drug was permitted to become effective on the basis of data demonstrating that, using the so-called mouse-uterine assay test, no res-

idues could be detected in edible tissue 48 hours after withdrawal of DES. NDA's for DES implants in cattle became effective in December 1955, again on the basis of mouse-uterine assay data demonstrating "no residue" under the permitted conditions of use. Applications became effective for DES in feed for sheep and as implants for sheep in 1957 and 1959.

The current standards for approval of new animal drugs, set forth in section 512 of the act as added by Pub. L. 90-399, July 13, 1968, 82 Stat. 343-351 (21 U.S.C. 360b), include several criteria. In addition to requiring substantial evidence of efficacy, section 512(d) makes very clear that the sponsor of any animal drug has the burden of demonstrating that the drug is safe for humans if encountered in food produced from the animal, and causes no adverse effect to the animal. Section 512(d)(1)(H) imposes additional restrictions on the approval of animal drugs that have been shown to cause cancer. That provision requires that FDA shall refuse to approve a drug if the Commissioner finds that "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 section 512 of the Delaney anticancer clause that was added to the act by the Food Additives Amendment of 1958.

In 1962, Congress enacted an exception to the anticancer clause. The focus of Congress at that time was so clearly on DES that this exception has ever since been known as the "DES clause." This exception, now also part of section 512(d)(1)(H) of the act, permits approval of the use of a carcinogen as a drug in animals only if the Secretary (by delegation under § 2.120 (21 CFR 2.120), the Commissioner of Food and Drugs) finds that:

... under the conditions of use 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 food yielded by or derived from the living animals.

In accordance with the foregoing provision, FDA in 1963 approved methods for the measurement and identification of DES residues: the mouse-uterine method, which measures total estrogenic activity at 2 ppb, and the so-called "paper chromatography" method, which is incapable of differentiating DES from other estrogens at levels below 10 ppb. Originally codified under §§ 135g.26 (b) and (c) and 121.241 (e) and (f) (21 CFR 135g.26 (b), (c) and 121.241 (e), (f)), the approved methods published in Part 135 were recodified under Part 556 without substantive change by a regula-

tion published in the *Federal Register* of March 27, 1975 (40 FR 13802). These methods have remained in effect since 1963, although significant improvements in sensitivity and reliability of other analytical methods have occurred in the intervening years.

Since publication of the detection methods in 1963, numerous new animal drug applications (NADA's) for the use of DES have been approved by FDA. In each instance, the agency concluded that if, when used in accordance with the conditions of use prescribed in the labeling, DES residues could not be detected in edible tissue by the approved methods, the requirements of the law were satisfied. Experience with the use of DES and advances in detection methodology have demonstrated that this conclusion is no longer supportable.

Since their original approval, no data have been submitted by the holders of approved NADA's for DES that cast doubt on the finding that the drug causes cancer in test animals. Furthermore, radioactive tracer research studies using ¹⁴C-labeled DES, conducted by the United States Department of Agriculture (USDA), have shown that radioactive residues attributable to the use of DES can result even when the prescribed conditions of use are strictly followed, i.e., withdrawal 7 days prior to slaughter for DES in feed or implantation of DES 120 days prior to slaughter. See T. S. Rumsey et al., "Depletion Patterns of Radioactivity and Tissue Residues in Beef Cattle after the Withdrawal of Oral ¹⁴C-Diethylstilbestrol," *Journal of Animal Science*, 40(3): 539-549, 1975, and T. S. Rumsey et al., "Fate of Radioactive Carbon in Beef Steers Implanted With ¹⁴C-Diethylstilbestrol," *Journal of Animal Science*, 40(3): 550-566, 1975 (available for public examination at the office of the Hearing Clerk, Food and Drug Administration). These radioactive residues were at levels that are below the sensitivity of the previously approved methods and that have not been shown to be safe within the meaning of the act.

In 1972 and 1973, the FDA, acting on these reports (then unpublished) of residues discovered by the USDA in radioactive tracer studies, withdrew all approvals of DES for use in animals used for human food. These actions were challenged by sponsors of NADA's for DES and ultimately vacated by the United States Court of Appeals for the District of Columbia Circuit in *Hess & Clark v. Food and Drug Administration*, 495 F. 2d 975 (1974), and *Chemetron v. Department of Health, Education, and Welfare*, 495 F. 2d 995 (1974) on the ground that the notice of withdrawal of approval issued by FDA had not afforded the sponsors adequate opportunity to demonstrate the need for a hearing, as required by 21 U.S.C. 360b(e)(1).

Since the resumption of the use of DES following the Court of Appeals' reinstatement of the NADA's, residues have been found in samples of edible tissues (livers) taken from cattle presented for

slaughter. In a USDA objective sampling program of cattle slaughtered throughout the country, 11 residues were detected in 2,854 samples in 1974 using gas liquid chromatography (GLC) methods. During the first 3 quarters of 1975, 25 residues were detected in 1,717 samples, indicating an increase in the percentage of samples containing DES residues from 0.41 percent to 1.46 percent. Two additional residues detected by USDA during the fourth quarter of 1975 in edible tissues of beef cattle are not included in the percentage calculation because the fourth quarter sample size is not yet known.

These calculations likewise do not include 17 additional DES residues found during 1974 and the first 3 quarters of 1975 in the USDA selective sampling program. This program samples on a non-random basis both animals presented for slaughter by raisers who have previously presented residue-carrying animals as well as animals that are suspected, on some other basis, of containing DES residues. In the selective sampling program, as would be expected, the incidence of residues is considerably higher.

Only 1 of the 36 residues detected in the USDA objective sampling program was at a level (greater than 10 ppb) that could have been both detected and identified as DES if the currently approved mouse-uterine and paper chromatography methods had been used. Furthermore, although FDA investigation of the causes of these residues indicates that several may have resulted from DES contamination of withdrawal feed or failure to follow the prescribed conditions of use of DES, a substantial number of the residues cannot be attributed to misuse.

In the face of these findings, it is clear that the central assumption underlying the previous approvals by FDA of DES for use in animals used for human food, i.e., that no residues would be detected when the drug was used in accordance with the currently approved conditions of use, is no longer valid. The currently approved methods for DES have been shown to be inadequate to detect significant residues. Residues being detected by other methods have not been shown to be safe within the meaning of the act. This showing was not previously required of the applicants since a common premise of all previous DES approvals was that no residues would occur. Moreover, since no level of DES residues has been proven to be safe within the meaning of the act, the Commissioner concludes that no new method for the detection of DES can now be approved pursuant to the 1962 exception to the anticancer clause.

INADEQUACY OF APPROVED METHODS

The Commissioner issued, in the *Federal Register* of March 27, 1974 (39 FR 11299), a proposal to revoke the approved methods for identification and measurement of residues of DES, and invited interested persons to comment within 30 days (extended 10 days to the close of business of May 6, 1974 by a

notice published in the *Federal Register* of April 25, 1974 (39 FR 14611)).

Sixteen comments were received on the proposal within the extended comment period: Six from manufacturers of DES, four from individuals, two from cattle industry organizations, two from cattle feeders, and one each from a citizens' association, and a scientific society. Eight additional comments were received after the comment period closed. Several comments supported the proposed revocation of the detection methods and urged the Commissioner to act to terminate the use of DES in food-producing animals, while other comments objected to the Commissioner's proposed action. None of the comments received supplied data or studies adequate to support the approval of any new analytical method(s), much less data or studies to demonstrate that the methods previously approved are adequate to detect residues of DES now known to occur.

All the comments may be seen at the office of the Hearing Clerk, Food and Drug Administration.

The comments received and the Commissioner's responses are discussed below.

1. Nine comments suggested that the official methodology might be an issue for a hearing rather than the subject of a revocation before a hearing.

The Commissioner notes that the designation of officially approved methodology does not independently require a hearing under the act. However, opportunity for hearing is required on the proposal to withdraw approval of the NADA's for DES, and any hearing held could include the issue of whether a practicable analytical method exists that is adequate to detect DES residues.

2. Eight comments stated that the use of DES was important to the revenue of cattle raisers and to the reduction of the cost of cattle production. Two comments stated that the revocation of DES approvals could affect consumer prices for beef.

The Commissioner notes that the economic importance of diethylstilbestrol to a particular industry or even its effect on consumer beef prices is not relevant to or determinative of the acceptability of detection methods offered to justify exception of the drug from the anticancer clause, nor is it relevant to the safety of residues resulting from the use of the drug.

3. Two comments stated that the present approved test-methods for DES are adequately sensitive. One of these comments limited its claim of adequacy to the use of the drug in implant form. The other stated that the sensitivity of the present methods is sufficient because the radioactive tracer studies that showed residues below the limits of the mouse-uterine test were discredited in court proceedings arising out of the agency's previous efforts to withdraw approval of these NADA's.

The Commissioner concludes that neither the scientific data cited in the proposal nor any information provided by this comment establishes any difference

between feed and implant uses of DES with respect to the adequacy of detection methodology. The Commissioner further observes that, whatever the deficiencies of other detection methods, there has been no showing that the approved methods are adequate to justify continued approval of DES. Neither comment submitted or referred to data that show that levels of DES below the sensitivity of the approved methods are safe within the meaning of the act.

4. Two comments stated that final action on the revocation of methods proposal should await resolution of the proposal on sensitivity of the method published in the *Federal Register* of July 19, 1973 (38 FR 19226).

The Commissioner notes that despite continuing efforts of FDA since that proposal to determine appropriate criteria for levels of sensitivity, the complexity and scope of the scientific and legal issues have combined to prevent completion of a final regulation to resolve the issues of methodology. No final regulation based on the Mantel-Bryan procedure is anticipated within the next 6 months. The Commissioner has concluded that the public and FDA should no longer await final action on that proposal before resolving the status of DES.

5. One comment contended that the GLC method, coupled with mass spectrometry identification, was superior to the present procedures, but the comment did not state that these procedures would be adequate to detect DES residues or provide data to support their adequacy. Another comment, while opposing any action to revoke existing methodologies, urged that if present methods were revoked they should be replaced with the GLC method as the official method and claimed that this method is sensitive to 0.5 ppb. This comment did not provide any information or data to demonstrate that levels of DES below 0.5 ppb are safe within the meaning of the act. Another comment stated that the GLC method reliably detects residues of DES as low as 1 ppb and noted that information describing this method had previously been submitted with an NADA. This comment, too, failed to provide data showing that a sensitivity of 1 ppb is sufficient to meet the requirements of the act or to show that residues of DES below 1 ppb are safe within the meaning of the act.

The Commissioner acknowledges that the results of USDA's GLC sampling program supply part of the basis on which he is proposing to withdraw approval of outstanding NADA's for DES. These results clearly demonstrate that the currently approved methods for DES, i.e., the mouse-uterine method and the paper chromatography method, are inadequate. The Commissioner concludes, however, that no showing has been made that the GLC method, whether used alone or in conjunction with mass spectrometry, may be approved in their place.

6. One comment stated that the burden of proof to demonstrate the safety of

DES should rest with those who wish to market the drug.

The Commissioner concurs with this comment and notes that Congress has placed the burden on the applicant to demonstrate the safety of any animal drug (21 U.S.C. 360b).

7. Three comments referred specifically to the Gass study cited in the proposal to revoke the methods for DES: Gass, Coats, and Graham, "Carcinogenic Dose-Response Curve to Oral Diethylstilbestrol," *Journal of the National Cancer Institute*, 33:971-977, 1964 (available for public examination at the office of the Hearing Clerk, Food and Drug Administration). The Gass study found that 6.25 ppb DES caused cancer in test animals (C₃H mice). Two of these comments claimed that this finding was a "false positive," one of them suggesting that another test animal should have been used instead of the mice that were used. Neither of these two comments provided data to demonstrate that DES does not cause cancer at levels of 6.25 ppb. The third comment questioned whether the Gass study was statistically sound and quoted two scientists who drew from that study widely divergent conclusions as to the lowest levels of DES capable of causing cancer. This comment concluded that this disparity of scientific opinion means that the present data are inadequate to determine safe levels and supports a request for additional funds to conduct more studies.

The Commissioner is of the opinion that, in the absence of convincing scientific evidence that the Gass study was in error or that there is some level at which DES is not carcinogenic, the determination that DES is carcinogenic in C₃H mice at 6.25 ppb cannot be ignored. The Commissioner agrees that data are not adequate to establish the lowest level at which DES causes cancer in test animals. The Commissioner is aware of no evidence that a level of DES that does not cause cancer in test animals can necessarily be assumed otherwise to be safe within the meaning of the act. On the basis of data currently available, the Commissioner questions whether any of the available analytical methods for the detection of DES residues affords adequate assurance that residues below the level of detection are safe within the meaning of the act.

8. One comment stated that one possible solution to the method suitability issue that should be explored would be to discard the livers of animals treated with DES.

The Commissioner is of the opinion that whether or not specific edible tissues may be discarded is not material to determining the adequacy of a method to detect DES residues in those or other edible tissues. It has not been demonstrated, for example, that DES residues in the liver may not serve as an indicator of residues present, albeit at lower levels, in other edible tissues.

9. Two comments suggested that the basic question of whether DES repre-

sented a public health threat as a carcinogen remained unanswered.

The Commissioner notes that the carcinogenicity of DES has long been recognized by scientists, and concludes that FDA need not await demonstration of a danger to public health before enforcing the act's requirements that animal drugs be shown to be safe and that any cancer-causing drug be demonstrated to leave no detectable residues.

10. Other comments, which opposed the administration of DES to cattle or its presence in any foods, pointed out that the Canadian Government had excluded United States beef failing to bear USDA certification that the animal had never received DES, and expressed hope that FDA would move expeditiously to remove DES from the food supply.

Although these comments are not directly relevant to the adequacy of the previously approved DES detection methods, they do support the agency's issuing of this notice of opportunity for hearing on the withdrawal of approval of NADA's for DES.

11. One comment suggested that in enacting section 512(d)(1)(H), Congress intended that carcinogens could be used in food animals and obliged the Secretary of Health, Education, and Welfare to establish some method of analysis.

The Commissioner disagrees. Section 512(d)(1)(H) of the act prohibits the use of any carcinogenic animal drug unless the Secretary makes certain affirmative findings, including a finding that no residue of the drug will be found in edible tissue by officially designated methods. Congress did not intend the Secretary to designate a method when no adequate method was available. Rather, the act requires that an animal drug not be approved unless an adequate detection method can be designated. To be approvable a detection method must be both practicable, in the sense that it must be adaptable for use as a regulatory tool, and it must be sufficiently sensitive. The Commissioner concludes that any method approved in accordance with section 512(d)(1)(H) must at least be capable of detecting residues at a level that has been shown to be safe within the meaning of the act. Because no such showing has been made with respect to residues of DES well below the combined sensitivity of the currently approved methods, the Commissioner maintains that those methods can no longer serve as the basis for approval of the use of DES in animals used for human food.

The Commissioner intends to revoke these methods at the time of final action based upon this notice of opportunity for hearing. If no hearing on the proposal to withdraw approvals for the use of DES is required, either because FDA receives no request(s) for hearing or because any request(s) for hearing fails to demonstrate a genuine and substantial issue of fact requiring a hearing, the approved methods will be revoked simultaneously with the announcement

of that fact. If a hearing is held, the currently approved method will be revoked, and any replacement method(s) demonstrated to be adequate will be designated at the time the Commissioner issues a final order based upon the hearing record and the decision of the Administrative Law Judge.

PROPOSED ACTION

On the basis of the comments received in response to the proposal to revoke the detection methods for DES, the data cited in the March 1974 proposal, and evidence that DES residues continue to be found in edible tissues of animals slaughtered for human food, the Commissioner concludes that:

1. DES has been shown to cause cancer in test animals and has been associated with the occurrence of cancer in humans.

2. Residues of DES have been and are being detected in the edible tissue of animals at levels that have not been shown to be safe within the meaning of the act.

3. The authority conferred by section 512(d)(1)(H) of the act to approve methods of examination allows, but does not require, the Commissioner to designate a method.

4. Any method designated by the Commissioner pursuant to section 512(d)(1)(H) must be practicable and capable of detecting drug residues regardless of the route of administration used for a drug.

5. The approved methods for detection of DES residues in edible tissue are not adequate to demonstrate that, within the meaning of the act, no residues will be found when the drug is used according to the approved conditions of use.

6. Data are lacking to justify the approval of any other analytical method(s) for detection of DES residues because no currently available method is capable of detecting residues at levels that have been shown to be safe within the meaning of the act.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(e)(1), 21 U.S.C. 360b(e)(1)), the Commissioner proposes to withdraw approval of all existing NADA's providing for the use of DES in animals used for human food on the following grounds:

1. Information and data available since these applications were approved, together with earlier data reevaluated in the light of current scientific knowledge, demonstrate that DES is not shown to be safe for use as approved.

2. The anticancer clause in section 512(d)(1)(H) of the act is applicable.

This notice applies to all outstanding NADA's for the use of diethylstilbestrol in animals used for food for human consumption. All such applications now known to FDA are listed below by NADA number and by each applicant's name and last known address in FDA records. Copies of this notice are being forwarded by registered or certified mail to each of these known applicants. Notice to other applicants or holders of such NADA's whose identity is not known to FDA is given by this publication.

NADA No. Name and address

8028----- Blanco Products Co., P.O. Box 1750, Indianapolis, Ind. 46206.

9757----- Pinner, Inc., 334 East 43d St., New York, N.Y. 10017.

9770----- See NADA 9757.

9758----- See NADA 9757.

10132----- Walnut Grove Products, 201 Linn St., Division of W. R. Grace Co., Atlantic, Iowa 50023.

10258----- American Cyanamid Co., P.O. Box 400, Princeton, N.J. 08540.

10261----- Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, N.J. 07065.

10421----- Dawes Laboratories, 460 State St., Chicago Heights, Ill. 60411.

10566----- Simonson Manufacturing Co., Quincy, Iowa 51048.

10964----- Vineland Laboratories, Inc., Subsidiary of Damon, 2285 East Landis Ave., Vineland, N.J. 08360.

11090----- See NADA 9825.

11295----- Hess & Clark, Division of Rhodia, Inc., 7th and Orange St., Ashland, Ohio 44805.

11856----- See NADA 9757.

11365----- E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, N.J. 08540.

11485----- See NADA 10421.

12553----- See NADA 11295.

14773----- Peter Hand Foundation, Inc., 2 E. Madison St., Waukegan, Ill. 60084.

15274----- O. M. Franklin Serum Co., P.O. Box 2335, Denver, Colo. 80222.

21446----- Fort Dodge Laboratories, Fort Dodge, Iowa 50501.

34735----- Standard Chemical Manufacturing Co., 701 S. 42d St., Omaha, Nebr. 68103.

34916----- See NADA 10421.

35017----- Thompson-Hayward Chemical Co., 3200 Specker Rd., Kansas City, Kans. 66106.

35019----- See NADA 35017.

36213----- Feed Additives, Inc., Fremont, Nebr. 68025.

36479----- S. B. Parick Co., 100 Church St., New York, N.Y. 10008.

36554----- Dale Alley Co., P.O. Box 444, St. Joseph, Mo. 64502.

36871----- See NADA 36554.

36975----- See NADA 34735.

37148----- National Oats Co., 1931 Baugh Ave., East St. Louis, Ill. 62206.

37541----- See NADA 37148.

37839----- See NADA 36213.

38507----- Texas Nutrition & Service Co., P.O. Box 5375, Fort Worth, Tex. 76108.

38509----- See NADA 38507.

38510----- See NADA 38507.

38582----- Ultra Life Laboratories, Inc., No. 1 Ultra Way Drive, Highland, Ill. 62249.

39161----- Square Deal Fortification Co., Kouts, Ind. 46347.

39491----- Brasley-Koeling, Inc., Ord, Nebr. 68952.

39715----- Feed Products, Inc., 1006 West 47th Ave., Denver, Colo. 80211.

39716----- See NADA 39715.

NADA No. Name and address

39717----- See NADA 39715.

39718----- See NADA 39715.

39772----- See NADA 10261.

40014----- Western Food Supplements, Ellensburg, Wash. 98924.

42162----- See NADA 9825.

42356----- Chemetron Corp., Chicago, Ill. 60611.

42702----- Farmland Industries, Kansas City, Mo. 64116.

42840----- See NADA 10261.

44344----- See NADA 11295.

44526----- Western Farmers Association, Seattle, Wash. 98111.

44793----- Palstar Brewing Corp., 5050 Oakland Ave., St. Louis, Mo. 63164.

45081----- See NADA 11295.

45082----- See NADA 11295.

Any holder of an approved application that elects to avail itself of the opportunity for hearing pursuant to section 512(e)(1) (21 U.S.C. 360b(e)(1)) and § 514.206 (21 CFR 514.206) must file with the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852, a written appearance requesting such hearing by February 11, 1976, giving the reasons why approval of the application should not be withdrawn, and providing a well-organized and full-factual analysis of the scientific and other investigational data such holder is prepared to prove in support of its opposition to the Commissioner's proposal. A request for hearing may not rest upon mere allegations or denials, but must set forth specific facts showing there is a genuine and substantial issue of fact that requires a hearing. Responses to this notice may be seen in the office of the Hearing Clerk during regular business hours, Monday through Friday.

If a hearing is requested and is justified by any holder's response to the notice of opportunity for a hearing, the issues will be defined, an Administrative Law Judge will be assigned, and a written notice of the time and place at which the hearing will commence will be issued as soon as practicable.

Any hearing on the withdrawal of approval of the foregoing NADA's will be open to the public. If, however, the Commissioner finds that portions of the applications that serve as a basis for such a hearing contain information concerning a method or process that is entitled to protection as a trade secret, the part of the hearing involving such portions will not be public, unless the respondent so specifies.

The Commissioner has carefully considered the inflation impact of this proposed action and a major inflation impact has been found, as defined in Execu-

tive Order 11821, OMB Circular A-107, and interim guidelines issued by the Department of Health, Education, and Welfare. Copies of the inflation impact statement are on file with the Hearing Clerk, Food and Drug Administration. The major conclusions found in the inflation impact statement are:

1. There are no satisfactory alternatives to the agency's proposed action that are consistent with the legal constraints imposed by the Federal Food, Drug, and Cosmetic Act, as amended.

2. Operating expenses to feed lot producers of cattle for feed and other items are estimated to increase by \$156 million during the first year following a DES ban. These increased costs are expected to fall substantially over the long term as substitutes to DES become available in greater quantities.

3. Retail prices of beef are estimated to rise by about 2 cents per pound, meaning the per capita cost of beef to consumers at current levels of consumption would increase approximately \$2 to \$3 annually. The aggregate consumer impact is estimated at \$503 million.

4. A ban on DES would not cause major inflation impacts, as defined by the HEW/OMB criteria, in the areas of competition, productivity, supply of materials, or use of energy.

5. The benefits from implementing the proposed action will be the elimination of any risk of cancer associated with the consumption, via the edible tissues of food-producing animals, of residues attributable to DES.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 512, 82 Stat. 343-351 as amended (21 U.S.C. 360(b)), and under authority delegated to the Commissioner (31 CFR 2.120).

Dated: January 7, 1976.

A. M. SCHMIDT,
Commissioner of Food and Drugs.
[FR Doc. 76-660 Filed 1-9-76; 8:45 am]

ADVISORY COMMITTEE Notice of Meeting

This notice announces a forthcoming meeting of a public advisory committee of the Food and Drug Administration. It also sets out a summary of the procedures governing the committee meeting and the methods by which interested persons may participate in the open public hearing conducted by the committee. The notice is issued under section 10(a) (1) and (2) of the Federal Advisory Committee Act (Pub. L. 92-463, 86 Stat. 770-776 (5 U.S.C. App. I)). The following advisory committee meeting is announced:

Committee name	Date, time, place	Type of meeting and contact person
Antibiotics in Animal Feeds Subcommittee of the National Advisory Food and Drug Committee.	Jan. 28 and 29, 9 a.m., Conference Room B, Parklawn Bldg., 5600 Fishers Lane, Rockville, Md.	Open committee discussion Jan. 28, 9 a.m. to 3 p.m.; open public hearing Jan. 29, 3 p.m. to 4:20 p.m.; open committee discussion Jan. 30, 9 a.m. until discussion of trade secret data; closed committee deliberations Jan. 30, discussion of trade secret data to adjournment; William V. Whitcomb, M.D. (HFG-1), 5600 Fishers Lane, Rockville, Md. 20852, 801-443-1547.