

PRECLINICAL AND CLINICAL TESTING BY
THE PHARMACEUTICAL INDUSTRY, 1976

JOINT HEARINGS
BEFORE THE
SUBCOMMITTEE ON HEALTH
OF THE
COMMITTEE ON
LABOR AND PUBLIC WELFARE
AND THE
SUBCOMMITTEE ON
ADMINISTRATIVE PRACTICE AND PROCEDURE
OF THE
COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE
NINETY-FOURTH CONGRESS
SECOND SESSION
ON
EXAMINATION OF THE PROCESS OF DRUG TESTING AND
FDA'S ROLE IN THE REGULATION AND CONDITIONS
UNDER WHICH SUCH TESTING IS CARRIED OUT

PART II

JANUARY 20 AND 22, 1976

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and the Committee on the Judiciary

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PRECLINICAL AND CLINICAL TESTING BY THE
PHARMACEUTICAL INDUSTRY, 1976

TUESDAY, JANUARY 20, 1976

U.S. SENATE,
SUBCOMMITTEE ON HEALTH OF THE
COMMITTEE ON LABOR AND PUBLIC WELFARE;
SUBCOMMITTEE ON ADMINISTRATIVE PRACTICE
AND PROCEDURE OF THE COMMITTEE ON THE JUDICIARY,
Washington, D.C.

The subcommittees met, pursuant to notice, at 9:30 a.m., in room 4232 Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittees), presiding.

Present: Senators Kennedy, Nelson, Javits, and Beall.

Committee staff present: Jay B. Cutler, minority counsel.

Senator KENNEDY. We will come to order.

It is now 6 months since witnesses from the Food and Drug Administration appeared before these subcommittees to raise serious questions about the integrity of the scientific data submitted to the FDA by the G. D. Searle Co.

The issues raised in July are at the very heart of the regulatory process. Although judgments in that process may reasonably differ, all judgments are made from the same foundation—scientific data.

If the integrity of that data is questioned, then the whole regulatory process is questioned. If the data are proven false and misleading, then the regulatory decisions may be tragically wrong. Accurate science is the best protection the American people have from an unsafe and ineffective drug supply.

Inaccurate science, sloppy science, fraudulent science—these are the greatest threats to the health and safety of the American people. Whether the science is wrong because of clerical error, or because of poor technique, or because of incompetence, or because of criminal negligence, is less important than the fact that it is wrong.

For if it is wrong, and if, as in this case, the FDA did not—indeed, under current practice, could not—know it was wrong, then the protective regulatory barrier between a potentially dangerous drug and the patient is removed.

In the last 6 months, at these subcommittees' insistence, the FDA has reviewed the raw animal data for seven of G. D. Searle's products. Their task force has done an exhaustive job. The Commissioner of the FDA has taken a close personal interest. He has kept these subcommittees fully informed.

He and his staff are to be commended. I would like to single out for special praise Dr. Adrian Gross, whose professional compe-

That is why these problems are so serious. That is why scientific integrity must be maintained. That is why these subcommittees will insist that the Environmental Protection Agency, the National Cancer Institute, the Consumer Product Safety Commission, and every other relevant Government agency do what the FDA is going to do—review the quality of their animal work; identify any problems; propose solutions and report back to these subcommittees. There is no activity which should receive a higher priority.

Senator Javits?

Senator JAVITS. Mr. Chairman, at the July 10, 1975, hearings, we heard dramatic, disquieting testimony respecting the integrity of the testing of new drugs by the G. D. Searle & Co.

This testimony regarding the validity of the data which supports applications to test and market a new product caused Senator Schweiker, the chairman and myself great concern. We recommended that the Food and Drug Administration Commissioner, Dr. Schmidt, initiate a full and complete investigation of the integrity of the animal data submitted by G. D. Searle & Co. to the FDA in support of the safety of its products.

While the final FDA task force report is not completed, I have reviewed the preliminary information presented in Commissioner Schmidt's prepared statement. It is deeply disturbing. The deficiencies exposed raise critically serious questions about G. D. Searle & Co. and the whole pharmaceutical industry, of which Searle is an important member.

The public has no choice but to be deeply concerned about whether the regulatory process—which requires that the private enterprise system must act in good faith—is, in fact, operating in the public interest.

This critical question is raised—to his great credit and commendation—by the Commissioner himself. In the draft of his prepared statement dated January 18, 1976, he states:

Are the problems found at Searle unique or industrywide? Do these findings cast doubt on the safety of our foods and drugs?

The first question—whether these problems are industrywide—we are not able to answer definitely at this point. Prudence dictates, however, that we assume the presence of an industrywide problem until proven otherwise, and our plans for the future are based on his assumption.

Dr. Schmidt may be assured that he will have my strong continued support in finding the answer to this critical question. The health and safety of the American people demand an effective FDA regulatory process.

The Commissioner's conclusion which would "require new Federal resources and be greatly aided by new legislative authorities" is an important first step in this direction. I urge him—as I did at the July 10 hearing—"to be an initiator in terms of recommendations to us, as to what ought to be done respecting the regulatory process."

Senator KENNEDY. We welcome back to this committee Dr. Alexander Schmidt, Commissioner of the Food and Drug Administration, who has appeared before this committee on a number of different occasions. We always find these appearances useful and helpful to us.

As I indicated in my opening statement, we want to express, from the committee's point of view, and I suppose from an individual's

tence, integrity and unyielding dedication to his job are primarily responsible for uncovering this problem.

There is much talk about bureaucrats these days—99 percent of it derogatory. I think the American people should know about Dr. Adrian Gross and the thousands of others like him in every branch of this government who work hard and well in service to the people of this country.

I have personally reviewed the findings of the FDA task force. I believe they cast doubt upon the integrity of the research program at Searle. Whether the programs at Searle are shared by other pharmaceutical companies is not clear. But I do not believe we can take that chance. These subcommittees will insist that the FDA immediately institute a program to review the work of the other drug manufacturers.

We stand ready to work to provide FDA with the resources it needs to do the job. We intend to monitor this activity and we expect the Commissioner to report back to us expeditiously.

We must know the extent of this problem, and we must know quickly. We cannot have millions of Americans taking drugs which were deemed safe on the basis of unsound scientific data. These subcommittees will press the FDA until the facts are known, the problems are identified and solutions are developed.

The importance of animal data to the health policies of this government extends far beyond the Food and Drug Administration. The National Cancer Institute, the Environmental Protection Agency, the Consumer Product Safety Commission—all depend upon animal data. This Nation is committed to an all-out effort to conquer cancer, to clean up the air and water, to detect and eliminate potential carcinogens from the environment. We cannot have these efforts undermined by unacceptable science.

The importance of research in these areas cannot be underestimated. Every day every American is exposed to a variety of potentially deadly substances. The exposure may be in the form of a drug taken over many years; it may be artificial colorings in meat; or pollutants in the air and water or additives in our food.

We must know what the long-term cumulative effects of these exposures are likely to be. Animal studies are an integral part of this research. If a drug causes cancer in animals, it is a serious warning. Physicians must be alerted. Use of the drug must be restricted. Patients must be informed of the potential risk.

Because so many of us are exposed to so many of these agents, the potential for extensive harm is great. We can get an idea of the problem from the DES tragedy; DES-caused cancer occurred years after the exposure, and in the offspring of the mothers taking the drug.

There is additional evidence from the current estrogen controversy. Used since the late 1930's, we are now told that Premarin is directly linked to cancer of the uterus. How many women are at risk? How many people would be at risk if best-selling drugs are shown to cause cancer 20 years after they are first taken?

There is a long list of potential killers. There is little conclusive scientific evidence now. If only a small minority of these potential problems occur, the results could be catastrophic.

point of view, the great appreciation that we have for the cooperation that you and your staff have provided this committee and for the diligence in the work that you have done in the review of this particular matter.

We look forward to your testimony here this morning. If you will introduce your colleagues; they are familiar. I think everybody has been here before; but if not, introduce those who have not been here.

STATEMENT OF ALEXANDER M. SCHMIDT, M.D., COMMISSIONER, FOOD AND DRUG ADMINISTRATION; ACCOMPANIED BY RICHARD A. MERRILL, GENERAL COUNSEL, FDA; RICHARD CROUT, M.D., DIRECTOR, BUREAU OF DRUGS; ROBERT C. WETHERELL, JR., DIRECTOR, OFFICE OF LEGISLATIVE SERVICES; CARLTON SHARP, SEARLE INVESTIGATION TASK FORCE; WILLIAM D'AGUANNO, PH.D., ASSISTANT DIRECTOR FOR PHARMACOLOGY-TOXICOLOGY, OFFICE OF SCIENTIFIC EVALUATION; M. ADRIAN GROSS, D.V.M., ASSISTANT DIRECTOR FOR SCIENTIFIC COORDINATION; PHILLIP BRODSKY, CONSUMER SAFETY OFFICER, INSPECTION BRANCH, PHILADELPHIA DISTRICT; AND RICHARD RONK, BUREAU OF FOODS, DIRECTOR, DIVISION OF FOOD AND COLOR ADDITIVES, A PANEL

Dr. SCHMIDT. I think all but one or two have been here.

On my immediate left is Mr. Richard Merrill, our General Counsel; on my right is Dr. Richard Crout, Director of the Bureau of Drugs; on his right is Mr. Carlton Sharp, who has headed our investigative task force; on his right is Dr. William D'Aguzzano from our Office of Scientific Evaluation; then at the end of the table is Dr. Adrian Gross, who is our Assistant Director for Scientific Coordination. On my far left, your far right, is Mr. Phillip Brodsky, who is a consumer safety officer from our Philadelphia district, who served as the field director for the recently completed investigations at Searle.

We are here this morning to discuss the quality of animal testing—

Senator KENNEDY. As I understand it, you have a more extensive and lengthy statement.

Dr. SCHMIDT. Yes, sir. I have a rather detailed and lengthy narrative statement which I would like to include for the record.

Senator KENNEDY. It will be included in the record at the conclusion of your testimony.

You have another statement that is quite extensive and complete and which I think is terribly important. There will be a few areas where I will ask you to elaborate, but we will see if we can continue the flow of the testimony.

Dr. SCHMIDT. Thank you.

With your permission, I will supply the long statement for the record and proceed with the shorter statement.

We are here this morning to discuss the quality of animal testing being conducted on products regulated under the Federal Food, Drug

and Cosmetic Act, and specifically, our investigation of Searle Laboratories.

The Federal Food, Drug, and Cosmetic Act imposed on manufacturers the burden of demonstrating that their products meet the safety requirements of the law. The Food and Drug Administration [FDA] conducts relatively little toxicology testing of its own and no clinical testing. Instead, we prescribe the type and extent of testing we believe necessary for a determination of safety and then review the data submitted by manufacturers to determine whether they meet these requirements. Thus, we require that all new drugs and food additives undergo extensive testing in animals to determine the fundamental toxicity profile of the compound, and particularly to determine whether they have any teratogenic potential, and to determine carcinogenicity whenever there is the likelihood of chronic exposure of humans.

Animal studies of human drugs are of particular importance in determining whether new products can safely be tested in humans to assess their potential therapeutic effect.

Because of the importance of animal toxicology data to our decisions, it is essential that these studies be technically complete, be conducted according to sound protocols, and be scrupulously controlled for quality.

At the July 10, 1975, hearing of these subcommittees, we described the questions that had arisen regarding the integrity of animal data submitted to us by the G. D. Searle Co. relating to the drugs, Flagyl and Aldactone.

From these preliminary investigations, we concluded that an in-depth study of the experimental animal operations of the firm was very much in order; and as you will recall from the hearing of July 10, 1975, we indicated we would investigate the animal studies submitted in support of Searle drugs marketed since 1968. Subsequently, we decided to include other Searle products, including the investigational drug Norpace and the food additive Aspartame.

To conduct the Searle investigation efficiently and expeditiously, an FDA task force was created in August 1975, to review the company's practices in conducting animal experiments, in analyzing the data, and in submitting this information to the FDA; determine whether any practices of Searle in conducting animal research are in violation of any laws; and recommend appropriate corrective action based upon the findings of the investigation.

The task force promptly prepared a plan for the investigation, and established investigating teams of well-qualified drug investigators and pharmacologists.

The task force then arranged for the review of all Searle submissions of animal data since July 1, 1968, to identify the laboratory which performed the study, its purpose, the animal species involved, duration, and the route of administration of the product; established criteria for selecting the products and studies to be investigated intensively; initiated an in-house review of the selected studies; on October 6, 1975, initiated the onsite phase of the investigation, with

teams going to Searle and Hazleton Laboratories simultaneously. The enormous task for reviewing the intimate details, involving literally millions of pieces of data, of the 25 selected studies continued until December 18, 1975.

During this period, the investigation teams generally spent 3 out of every 4 weeks at Searle or Hazleton, often working 18 hours a day.

I would emphasize, because I think the point will come up later, the tremendous amount of work that has been accomplished in reviewing these 25 studies.

At the present time, the task force, with the assistance of a group of pharmacologists, is still analyzing the data contained in the draft reports. Therefore, the findings that I will describe shortly must be considered as subject to some modification.

In addition, the distinct possibility of legal action growing out of this investigation requires that some of our findings be described only in general terms.

Once the final review has been completed, any necessary followup on the completed studies will be undertaken and the task force will prepare a final report and recommendations. In the meantime, consultation will soon begin with the Department of Justice to assure that all relevant material is available to them when we reach final decisions on the appropriateness of regulatory action.

Senator KENNEDY. Are you sending the material there?

Dr. SCHMIDT. Yes, sir. We have decided, as we proceed through the final stages of our evaluation, that we would consult continuously with the Justice Department, and have been in contact with them and will continue to work with them in the evaluation of our findings.

Now, in regard to the investigation in general, we found, regretably, that the required attention to detail in conducting these animal studies is sometimes lacking. For some time, we have been concerned about the absence of industrywide standards, and the lack of a systematic Federal inspection program for toxicology laboratories. The importance and complexity of these studies are by themselves sufficient reason to recommend such a program. But in addition, there is now growing evidence of significant quality-control problems in these laboratories. Some of this evidence comes from our Searle investigation.

Senator KENNEDY. Do you believe there to be a general problem throughout the industry?

Dr. SCHMIDT. We believe at this time, on the basis of the limited evidence that we have from our own inspections, that there is some degree of a generalized problem. We are not yet in a position to describe factually and in detail the extent of an industrywide problem.

We believe that certainly not all laboratories, not all pharmaceutical firms have had all of the problems that we found at Searle. But we do believe that there are general and industrywide problems in conducting, in planning and carrying out and reporting these kinds of studies.

One of the things that we intend to do is to systematically sample the universe of drug firms, contract laboratories and others to deter-

mine factually what kind of problems exist and how extensive they are.

We intend to do this in conjunction with other Federal agencies.

Senator KENNEDY. I understand you will make some specific recommendations on this point a little later in your testimony; but as I understand from this point here, you are sufficiently concerned about this particular issue from an industrywide position that you are going to take steps to review industrywide the animal studies which, in this particular case with regard to Searle, you found to be so bothersome, troublesome and distressing?

Dr. SCHMIDT. In general; yes.

I think that we simply do not have the resources to evaluate all animal studies of all contract laboratories and pharmaceutical houses. What we intend to do is to set up scientific and systematic sampling of the universe of the people who do these studies. That will tell us whether there is a serious industrywide problem or whether the laboratories and firms are distributed on a curve, some better than others, which is what I would suspect.

Senator KENNEDY. We recognize that you cannot do all these various drugs; but there is no reason that you cannot test at least the ones which are being used to the greatest degree.

Dr. SCHMIDT. In selecting the drugs that we looked at in the Searle Lab, we set up some interesting criteria for selecting drugs to look at which pose the most risk to individuals taking them. This is described in my longer statement.

We would use the same kind of a screening process for selecting those drugs and those pharmaceutical houses for a serious look at their animal work.

Senator KENNEDY. But as a potential problem, you are sufficiently concerned and distressed, based upon what you found in this particular investigation as well as its relationship to other submissions, by other companies; that you believe it is of prime importance in terms of the role of your agency as well as others?

Dr. SCHMIDT. Yes, sir. Our priorities are first to complete very quickly the Searle investigation and then immediately to move on to survey other firms and contract laboratories.

Senator JAVITS. Mr. Chairman, would you allow me to break in at this point just for a request?

I would suggest, Commissioner, that to assist our Chairman who is so ably carrying this on as is our ranking member, Senator Schweiker, and myself and others, that at the same time that you come to us with your report, you request the additional resources which will enable you to do what has to be done.

I am very alarmed by your testimony, obviously; but even more so by the fact that on so critical a matter, the resources of the FDA should be insufficient to do what the public interest may require.

So if you would be kind enough, Commissioner, to ask us for what you need, it would be our duty to do our best to get it in time rather than just to have you feel limited because you do not have the resources.

Senator KENNEDY. Would the Senator yield?

Senator JAVITS. Yes.

Senator KENNEDY. Maybe rather than what you say you need, you would tell us what you requested from OMB. I think that might be somewhat simpler.

Senator JAVITS. I would accept that very enthusiastically.

Dr. SCHMIDT. I would be very happy to do that.

Senator JAVITS. It pleases everybody.

[The information referred to follows:]

FOOD AND DRUG ADMINISTRATION ADDITIONAL BUDGET REQUEST FOR FISCAL YEAR 1977

Budget appendix page	Heading	1977 request pos.d.og	1977 proposed amendment	1977 revised request
323	Salaries and expenses.....	\$223,155,000	\$16,388,000	\$239,493,000

The additional amount requested will fund a comprehensive new Food and Drug Administration program to monitor the conduct of tests by industry to determine the safety of human drugs and food additives. Recent investigations have revealed serious deficiencies in the testing of new drugs and food additives. It is necessary that these deficiencies be corrected. To assure the safety of drugs and food additives, the proposed program will provide close monitoring of preclinical and clinical testing of drugs and food additives and reevaluation of currently used food additives.

Senator KENNEDY. As I understand, even though OMB in the last few hours—really, the last 48 hours or so—has indicated, at least in your testimony, that those aspects where you talk about what might be needed to accomplish this particular job were actually deleted from your testimony—

Dr. SCHMIDT. As I am sure the subcommittee knows, the Administration's request for resources and legislative authority are cleared through OMB. That was done in this case. What is in the testimony is what was cleared by OMB.

Senator KENNEDY. It was done in this case. I think that both in the course of the hearings that we are going to have today and the remainder of the week, it will be pointed out, probably as dramatically as at any hearings that we have had, the importance of getting adequate resources for your department to protect the health of the American people. And you can tell from what Senator Javits said this morning, and it is certainly my own view, that we want to make every effort to insure that you are going to get the resources on it. We will get that from you later. But we want to continue the hearing now, and we want to get specifically the request that was made from OMB.

Dr. SCHMIDT. Thank you.

In the longer statement I have included considerable detail regarding our findings on specific products.

At this time, I will simply highlight here some of the task force findings on some of the products selected for review, including the drugs Aldactone and Flagyl and the food additive Aspartame.

The investigation of Aldactone consisted of a detailed review of two studies, the 78-week rat carcinogenicity study discussed at the July 1975 hearings before these subcommittees, and the 104-week rat carcinogenicity study conducted by Hazleton Laboratories.

On July 15, 1975, following the hearings, Searle revealed to us the existence of a pathology report on this study from Microscopy for Biological Research Ltd. (MBR) which had been submitted to Searle in March 1973, but had not previously been disclosed to FDA.

This report clearly indicated a dose-related increase in the frequency of liver and testicular tumors and recommended that these findings be analyzed for statistical significance.

Although FDA regulations require "alarming findings" to be submitted to the Agency promptly, this had not been done.

In the course of our review of the 78-week study on rats, we have found a variety of other problems and questionable practices. For example, tissue masses were excised from three live animals during the study, and the animals were allowed to continue in the study. Two of these tumors were malignant and were not reported to FDA.

Senator KENNEDY. Is it not true that malignant mammary tumors were not reported? Those were mammary tumors, as I understand it, on your own findings on Aldactone? As I understand, on page 4, it says, "Omission of malignant mammary tumors from statistical summary submitted to FDA."

Dr. SCHMIDT. That is correct.

In general, when tissues were examined by a surgical incision or removed, these were palpable tumors in the stomach of the rat.

Senator KENNEDY. Is this not particularly significant with Aldactone, this question of the mammary tumors?

Dr. SCHMIDT. Yes; it would be significant in any case; but it relates to the questions that had arisen about Aldactone.

Senator KENNEDY. And this, as I understand—the issue about the potential, about the danger of mammary tumors—was raised within Searle back in 1971 on Aldactone in general by Dr. McConnell? You are familiar with that memorandum where he said:

I suggest strongly that the mammary gland receive the attention that it has long deserved and now demands, in terms of research efforts and research dollars. Knowledge of the pharmacologic and toxicologic propensities of the female and male breast, both laboratory animal and man, may well exert a major impact on the sale of established and new products, especially steroids.

It goes on, "Thus, I propose that now is an appropriate time for devising and implementing a program in comparative mammology and chemically induced mammary lesions."

[The memorandum referred to above follows in its entirety:]

RRPA 37

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113090

December 16, 1971

MEMO TO: Dr. Koe
 COPY TO: Dr. Matting
 FROM: Dr. McConnell

→ S. E. M.

PLR Exhibit 72
 Mr. Seale Labs -
 Schieffelin
 Date 10/6-12/5/75
 Inspector CHE/SLS/CGO

SUBJECT: Short Treatise on the Mammary Gland (Breast); its Importance in Preclinical and Clinical Drug Safety Evaluations and in Maintaining any Given Drug on the Market.

I suggest strongly that the mammary gland receive the attention that it has long deserved and now demands, in terms of research efforts and research dollars. Knowledge of the pharmacologic and toxicologic propensities of the female and male breast, both laboratory animal and man, may well exert a major impact on the sale of established and new products, especially steroids.

Several separate problems or situations combine to emphasize the need for prompt attention to this area, namely:

1. Recognizing the very low incidence of breast neoplasms, benign or malignant, in the human male, it becomes quite apparent that the detection of such a growth in even one patient in a study group treated with a chemical agent would, epidemiological significance notwithstanding, almost certainly be interpreted as being chemically-induced. The detection of early neoplastic and of pre-neoplastic changes is generally related to the extent and the depth of clinical examination procedures employed; the more frequent and detailed (e.g. biopsy of firmness or small nodules) the exam, the higher the incidence of pre-neoplastic and early neoplastic change. The implication for the Aldactone-gynecomastia problem is quite apparent.
2. The problem of mammary tumorigenesis in dogs treated with xxx various oral contraceptive agents needs no further elaboration.
3. Various regulatory agencies have periodically expressed the desire for preclinical evidence of the effect of a given agent on mammary gland function; the FDA is currently considering this subject. In addition to morphologic examination of the mammary gland in all toxicology studies, I would anticipate a requirement for direct or indirect data on mammary function

December 16, 1971
Page 2

E.I.R. Exhibit 72
 Mfg. Searle Labs
 Date _____
 Inspector _____

in the relatively near future. Methods suitable for such studies would no doubt also be applicable to studies searching for an animal model of gynaecomastia. They would also aid immeasurably in selecting or rejecting animal species for toxicological studies designed to predict safety in the human.

4. A crisis in experimental and clinical oncology relating to the role of environmental chemicals in cancer etiology has developed nationally, as you know. A major emphasis is on detecting tumorigenic chemicals and promptly removing them from the human environment. Thus, all short-term studies (e.g. gonadotropin - hormone balance) that might reliably predict or even provide suspicion of a carcinogenic or co-carcinogenic effect would be most valuable in selecting compounds for further development.

Thus, I propose that now is an appropriate time for devising and implementing a program in comparative mammary and chemically-induced mammary lesions. Data on the relationship of hormone balance to eventual mammary lesions (e.g. gynaecomastia and tumors) would be valuable and perhaps even critical to several drug development programs. We badly need scientific enlightenment in this area.

The relative importance of this program deserves careful consideration; it could be implemented with existing personnel, subsequent to rearrangement of some existing priorities. I have periodically stressed my concern with this area over the past several years; this concern mounts. Over the past three years, we have lost a promising anti-ulcer drug candidate (SC-15396) due to mammary tumor induction in the rat, we have remained on pins-and-needles due to potential mammary problems in the long-term safety studies of oral contraceptives in dogs and monkeys, and have incurred a serious clinical liability (gynaecomastia) in the Aldactone program. I reiterate, we need some scientific knowledge and know-how in experimental and clinical mammary.

R.G. McConnell

RGRSC:m1

Senator KENNEDY. As I understand, back in 1971 this particular drug was flagged, so to speak, about the dangers of the potential formulation of mammary gland tumors; that later the studies themselves were submitted to you and that two of the tumors that were actually malignant and were mammary tumors were actually not reported to the FDA.

What does that sequence of events indicate to you?

Dr. SCHMIDT. Well, the December 16 memorandum clearly indicates a proper concern for the meaning of "breast tumors," and particularly involves drugs which may have the side effect of swelling of the breast, in particular, steroidal drugs. So I think the concern of the individual writing the memorandum was quite well placed.

This, though, is set alongside a practical problem of really not looking at the significance of actual tumors with enough care or not thinking it important to report these in all instances to the Food and Drug Administration.

Senator KENNEDY. Well, there is a little bit more of a sense of urgency than that, is there not, Commissioner? They flagged it about the dangers—their primary medical personnel flagged it about the dangers of the formulation of mammary gland tumors, and then at the time when they did a study, the results of which they submitted to you, tissue masses were excised from three live animals during the study and the animals were allowed to continue in the study, and two of the tumors were malignant.

These happened to be malignant mammary tumors. They were not reported to the FDA. I would think that is rather an important matter. Certainly it is. I would think, from your own kind of evaluation of the animal. Would it not be so?

Dr. SCHMIDT. It is indeed important.

Senator KENNEDY. All right.

Dr. SCHMIDT. After we began our on-site investigation of the 78-week rat study, the firm presented three volumes of Corrected and Expanded Reports. The volumes were prepared by a group of Searle scientists to identify differences between the initial reports submitted to the FDA and the actual raw data.

It is disconcerting that even today, after three separate reviews by Searle personnel of the same data from the 78-week rat study, we are continuing to discover errors that complicate review of this study.

Review of a 104-week rat study on Aldactone conducted at Hazleton Laboratories also revealed problems. Only 70 percent of the tissues scheduled for histopathological examination in the protocol were actually examined. In addition, some animals with gross lesions which, according to the study protocol, required histopathological examination, were not so examined.

Senator KENNEDY. What is Hazleton Laboratories?

Dr. SCHMIDT. My understanding is that this is a private laboratory that does contract research for a variety of contractors, including the Government and private industry.

Senator KENNEDY. It does not do research just for Searle? It does it for a number of the companies, is that right?

Dr. SCHMIDT. Yes; it does work for a number of Government agencies and a number of members of different kinds of industry.

drug industry and chemical industry and so on. It is a member of a group of contract laboratories that have sprung up around the country as a result of regulatory requirements in good part. They are profitmaking research organizations that perform required research in many instances.

Senator KENNEDY. They do work for the Cancer Institute as well?

Dr. SCHMIDT. I believe so; yes.

Senator KENNEDY. So they do it for a number of the companies, including a number of the governmental agencies, is that correct?

Dr. SCHMIDT. Yes, sir.

Senator KENNEDY. All right.

Dr. SCHMIDT. Moving then to the drug Flagyl.

The investigation of Flagyl included detailed review of the 80-week rat carcinogenicity study discussed at the July hearings and five studies dealing with the effects of the drug on reproduction and fetal development.

The investigation has disclosed that reports on tumors in the animals of this study were submitted to FDA in 1969, 1970, 1974, and 1975. Prior to 1975, each of these reports differed from the others in the number of tumors reported.

Senator KENNEDY. What is the significance of this?

Dr. SCHMIDT. Well, the significance is that one does not really know how many tumors to include in the calculations of the study results; and it indicates some problems, obviously, in recordkeeping and calculation.

Generally, difficulties in correcting things adequately means inadequacies in the raw data that one turns back to for answers.

I think one of the problems we have had is reconstructing what really happened from the raw data sheets which, in many instances, are either inadequate or inaccurate as found by talking to the people who recorded the observations in the first place.

Senator KENNEDY. Well, I suppose the matter which is most bothersome and distressing is that you are getting conflicting conclusions in terms of the statistical studies. That has to be a matter of very major importance and significance, is it not? Do you not consider that to be the case?

Dr. SCHMIDT. I would certainly agree; yes, sir.

Senator KENNEDY. That is really what we are talking about in this case here: am I correct?

Dr. SCHMIDT. Yes. Perhaps Dr. Gross, or others, could comment on this. In some instances we were not able reliably to reconstruct the actual numbers to be derived from experiments. This, of course, renders at the very least the value of the study much, much less than it ought to be.

Among additional major findings of the investigation of this study are: (1) For several of the animals, it was noted that the microscopic examination of tissue slides had been conducted by two different pathologists at Searle who reported different findings. Rather than submitting both reports, or having a third pathologist review slides on which the first two disagreed, Searle submitted only the second pathologist's report, which in our view appears substantially more favorable to the drug; and (2) Searle employees were unable to

explain many of the procedures by which microscopic findings were recorded, edited and verified prior to the inclusion in the report of this study; most records of observations of microscopic findings were not dated or signed. They were also unable to account for the differences in raw data and the final reports submitted to FDA.

Senator KENNEDY. You mean final reports did not reflect the raw data?

Dr. SCHMIDT. In some instances this is true; and of course we tried then to discover the reason for the discrepancy between summary results that were submitted to us and the raw data.

In some instances we were able to discover the error made and in other instances these discrepancies remain a mystery.

Significant problems were also encountered during the review of five reproduction and teratology studies of Flagyl.

For only one of the studies could a protocol be found, and the study, as conducted, showed significant deviations from the protocol.

Calculations made by the investigation team indicate that the animals received a lower dose than reported, which could convey a misleading favorable impression of the toxic potential of the drug.

It was impossible in some cases to be certain animals had received the amount of drug intended. Animals were dropped from one study without explanation, mating observations unrecorded, and autopsy records not maintained.

Senator KENNEDY. All of this is really another mistake, I imagine, in favor of the company and approval of the drug?

Dr. SCHMIDT. In a number of instances, we believe that mistakes made favored the drug, and in one or two it did not. And some we are unable at this point to say.

Senator KENNEDY. Yes; but most of the mistakes, as I understand, from the review of your testimony, were made in favor of the drug?

Dr. SCHMIDT. In some instances this is true; yes.

Senator KENNEDY. Is it? Just in some instances? Did you reach any conclusion whether more were made that would actually favor the drug?

Dr. SCHMIDT. I can only answer this at this time---

Dr. Gross, could you answer?

Dr. Gross. We have not made an exhaustive balancing of what mistakes there were. As the Commissioner reported, mistakes were made in both directions; but we have not reached a complete audit.

In the case of the two pathologists looking at the same slide, it is true, as the Commissioner stated a minute ago, that the report submitted to us would seem to be more favorable in general to the drug.

Senator KENNEDY. Well, the answer I was looking for, as I understand it, page 11, point No. 3, you say:

"Many decisions made in the course of designing, conducting and reporting studies tended to minimize the chances of discovering toxicity and to allay possible SBA concern."

This is your conclusion?

Dr. SCHMIDT. That is correct. And in this instance, I would be terribly upset with the mistake favoring the drug; but I am mainly upset by the simple finding of all of these errors and improper practices; and that really is a significant enough finding.

Moving then to the food additive, the sweetener Aspartame. More than 160 studies were submitted by Searle in support of the food additive petition for Aspartame, a sweetening ingredient. Of these, 11 were selected for review. Again, I will summarize some of our findings.

In a 115-week rat study, we noted numerous problems, including poor methods of distribution and identification of control and treated animals, poor records of weighings, and no assays of homogeneity of the product with the diet.

Approximately 90 of the 196 animals that died during the study were fixed in toto and necropsied at some later date: in some cases more than 1 year later.

Records indicated that a high-dose female found dead during the experiment contained a tissue mass. The submission to the FDA reported no such tissue mass, and the animal was excluded from the study due to marked autolysis.

Records of a number of animals disclosed significant discrepancies between recorded gross observations and the individual pathology summaries submitted to the FDA. In other instances of questionable practices, tissue masses were visualized through skin incisions—a highly unusual practice.

As I mentioned before, these were principally breast masses that were examined.

Review of five reproduction and teratology studies for Aspartame revealed poor animal husbandry practices and problems in the design of some of the studies. I will not go into the details of this, but I would simply observe that a consultant in a letter to Searle questioned the shaky foundation laid by the studies.

Senator KENNEDY. As I understand—this is very brief, and we will include it all in the record—is a brief comment:

Have spoken to Dr. Palmer on this study. It is review of study of lengthy report. He will airmail further copy to McConnell immediately. Overall comment is as follows: He would not take much notice of very many of the studies because of bad experimental design, animal husbandry and statistical analysis. He feels only useful study was the first dietary study which demonstrated that it is impractical to administer APM in the diet.

This is, as I understand it, the consultant that was hired by Searle to review the work, the quality of the work: and that is his conclusion as commented on by the Searle representative.

Is that basically what you understand to be the case?

Dr. SCHMIDT. Yes, sir.

This was followed up by more lengthy evaluation that did arrive, that we then turned up in the investigation, which in essence, confirms the initial report.

One final example with regard to Aspartame: Our investigators found that a pathologist's summary was edited in such a manner as to alter, generally in a favorable direction, some of the pathologist's summarized findings. The original report was not submitted.

Senator KENNEDY. Just before we go on, obviously we have been reviewing the scientific data that has been developed and submitted and in many instances, at least in some instances, as your own testimony points out, unreported, misreported, altered or changed. As I

understand, then in addition to types of scientific data that were submitted, there was apparently an additional strategy by the company. I would be interested in whether you run into this kind of a problem in terms of this company or other companies. In connection with Aspartame, a memorandum that was apparently sent to the top members of the company who were working on this drug.

I will include the whole document in its entirety in the record. But it says in one paragraph:

At this meeting, the basic philosophy of our approach to food and drugs should be to try to get them to say "Yes," to rank the things that we are going to ask for so we are putting first those questions we would like to get a "yes" to, even if we have to throw some in that have no significance to us, other than putting them in a yes saying habit.

We must create affirmative atmosphere in our dealing with them. It would help if we can get them or get their people involved to do us any such favors. This would also help bring them into subconscious spirit of participation.

And it mentions two of the officials.

[The letter and memorandum referred to follow:]

December 18, 1970

MEMORANDUM

TO: Dr. Lizard
Dr. Cline
Dr. Jenkins
Dr. Roe
Mr. O'Bleness

VOLUNTARY SUBMISSION

CONFIDENTIAL - Trade Secret Information

FROM: Mr. Helling

SUBJECT: Food and Drug Sweetener Strategy

These are thoughts on the matter of sweetener strategy. As I see it, our objective is to obtain approval from the Food and Drug Administration for SD-13.62 for enough uses to permit consumption (and hence production) at a level that will meet the economic requirements. With that in mind, we have to say what we need to do, know, or accomplish in order to bring about this objective.

We must determine which application of the sweetener seems possible and then select from those those that seem most likely to be approved. We must do this on a few categories of food categories basis for now as price will become a factor as you said on. We must then estimate the consumption potential and what portion of this we think we could get for out of those uses to get a projected consumption level; this will allow us to estimate selling price at each aggregate level of consumption (production).

We must decide what factors Food & Drug would be most concerned about and determine what of those food items would present the least serious concerns (after ranking the concerns in order of our difficulty to meet at this time).

We should arrange an early informal meeting with Dr. L. Hilda and Dr. Blumenthal. At this meeting, the basic philosophy of our approach to Food and Drug should be to try to get them to say "yes" and to make the things that we are going to say for so that we are putting forth those questions that we are likely to get "yes" to, even if we have to throw some in that have no significance to us or a team policy that into a yes-saying habit. We must create an affirmative atmosphere in our dealing with them. It will also help if we can get them to get the people involved to do us any sort of favor at this point also help bring them into a subconscious spirit of participation.

My price concern at this time is with the production of SD-13.62. We have our lack of complete, comparable data on SD-13.62. We need to get this completely to D&F. If we select facts that have their own, in any form, particularly if they are formulated so there is an audit

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ingredient, then we would have confidence that the SC-10262 would not break down measurably during the usual maximum storage periods. We then must consider how much BWP could be formed from the time the system is converted to a wet system to the time of consumption allowing for maximum likely abuse. In this way, I would say that the first category of items for which we should seek approval would be those applications where the sweetener is used and held in dry form and consumed within an hour of solution, where no heat is involved. An illustration of this is a pre-sweetened cereal product that's consumed cold. A second category would be where the sweetener containing composition is held dry and consumed within about an hour, but heat is involved. An example of that is a mix that is pre-sweetened such as a chocolate drink or tablets for table use; I exclude from this the table top sweetener. The next category would be where the acid food is kept cold but for periods of more than a few hours and no heat used in its preparation. For example here would be a Kool Aid product that would have a maximum likely exposure of about one day unrefrigerated and perhaps as long as a week refrigerated. For this, as an acid product, we would expect good stability, but we must be prepared to have actual data on BWP formation during one week's refrigeration storage or 24 hours at say 30°C before we proceed to Food and Drug. The next category is an acid product that is kept cold but might involve heat in its preparations such as a gelatin dessert; the maximum likely exposures would be like Kool Aid and I think that we should run data here too. The next category that I would think would be worth looking at would be a non-acid product stored cold that involved heat such as a non-instant dietetic pudding or a pre-sweetened hot cereal. Somewhere in here we would be also trying to fit in such things as the non-dry, but still essentially non-aqueous systems such as bacon and the products that are stored frozen that are heated and consumed immediately and then the products that are stored frozen that are cooked and not consumed immediately and so on.

In effect then, I would first ask for an informal, but not necessarily off the record meeting. As a basis for this meeting, we would present a series of assumptions. These assumptions will be specifically stated and any informal non-binding opinions would be predicated on the basis that we can, or our friend Ed, convince them that the assumptions are true. I would first make the assumption that the material is stable in dry form and that therefore the BWP exposure is limited to about 2% which is the normal concentration level in the sweetener. I would not at this time raise the question of restrictions on essential and non-essential amino acids, but I would be prepared to respond if they raised it at this time and would certainly want to raise it before the day was out. Once we've gotten this far, I would want to establish that, with the level of sweetener, as it's normally composed including the BWP, and with the toxicity data that we have in the feeding studies, we expect to get approvals now on the basis of the data on hand. We would have to be prepared with the average intakes of the sweetener that might

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CONTAINS THE FOLLOWING INFORMATION

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re involved and maximum likely intake involved in the presumed cereal type use. I would proceed to the next food category, and take these food categories one at a time to see where we begin to meet resistance. Where we meet resistance, having the data on average and maximum likely exposure for each of the uses that we bring up, then I would want to explore the nature of the resistance and what we would have to do to overcome it, particularly in relation to studies that are going on.

I think that it's vital to point out to the Food and Drug people at this meeting that the sweetener is not suitable for all applications for artificial sweeteners and at best would only be functional in part of the market that was held by cyclamate or saccharin. The approach from the meeting standpoint must be made to Dr. Virginia Solnick, head of the Bureau of Food, who is from an industrial background and whom Dr. Scott feels is quite good.

With the spot-for-spoon, we have no way of estimating maximum likely abuse and hence need to utilize data based on almost complete conversion to DCP. If we include this use in the original FAP, we stand a good chance of ending up with nothing in the short run and nothing in the long run whereas the other approach would give us something in the short run and, quite likely as much as we would ever get in the long run. I think it becomes very important for us to start to get our sweetener into commercial channels as soon as possible to minimize the incentive that people now have to work on other sweeteners. Actions in the U.S. will tend to influence the actions in other countries as well.

H. H.

Herbert Halling

HL:jed

VOLUNTARY SUBMISSION

CONFIDENTIAL - Security Information

I understand that the real question in terms of trying to make judgments on these matters supposedly would be based on scientific data and only scientific data, not just a general kind of willingness to get into a subconscious spirit of saying yes.

Do you find these efforts by the company to be effective? Are there similar efforts made by other companies to your knowledge?

Dr. SCHMIDT. I was interested by the discovery of this memorandum. In a sense, I was not surprised.

Senator KENNEDY. What do you mean by "not surprised"?

Dr. SCHMIDT. Well, I have observed over the years that in many pharmaceutical houses that there is a conflict between the scientific side of the house, if you like, and the marketing side of the house. A pharmaceutical firm is, after all, an interesting mix of legal people, marketing people, advertising people and scientific people. They are often contesting approaches and other ideas within the organization. And at times the scientists hold forth and at other times advertising people or marketing people hold sway. This impacts heavily at times on what a pharmaceutical house does.

This memorandum to me is rather a misguided attempt, I suppose, at planning. I would not be surprised if there was a similar memorandum about coming here before this subcommittee.

I would guess there are a lot of meetings going on in companies planning how they are going to deal with the FDA, how they can persuade the FDA, and how their views can carry the day at FDA.

I think there are a bunch of hardnosed people in FDA, and I have not observed anybody with the habit of shaking his head up and down like this [indicating].

In a sense, this is a silly memorandum. I would be embarrassed by it.

Senator KENNEDY. Well, it may be a silly memorandum, but I suppose the real issue is the effect that any of these techniques have on the FDA. Evidently they believe that it does have some impact or some positive effect on it. To the extent that it does or does not I think is a matter of concern, I suppose particularly when we are considering the kinds of scientific data which has been found wanting and lacking in this case.

Dr. SCHMIDT. Yes.

Senator KENNEDY. Furthermore, one document that was submitted with regard to various animals—and I have the list of the various animals that were included in a variety of different tests, there were about 24 or 25 of them—on this particular list, of the 24 or 25 animals, a number of them are each considered to be alive and then dead, and then alive and then dead again, for the purposes of reporting.

One here, the number is A15MM. It says, "Found dead March 13, 1971; alive April 3, 1971; dead June 1, 1971; alive August 23, 1971; dead September 20, 1971."

Now, this is not just one animal; this is repeated in others. Some have vanished. Some were alive, such as K18LF—"Alive April 22, 1971; vanished on May 20, 1971; and alive June 17, 1971"; and then he is vanished again on July 15, 1971.

[The list referred to follows:]

Final List of Animals by Letter and Number Involving a Variety of Different Tests

J24HM	Found dead	3/21/71	B19HF	Alive	6/29/71
	Alive	5/19/71		vanished (dead ?)	7/27/71
	Dead	6/16/71		Alive	8/24/71
	Alive	7/14/71		vanished (dead ?)	9/21/71
	Dead	8/11/71		Alive	10/19/71
				vanished (dead ?)	11/16/71
				Alive (?)	2/22/72
K18LF	Alive	4/22/71	E21HF	Found dead	2/25/71
	vanished (dead ?)	5/20/71		Alive	8/24/71
	Alive	6/17/71		Dead	9/21/71
	vanished (dead ?)	7/15/71		Alive	10/19/71
*M25CF	Found dead	3/ 6/71		Dead	11/16/71
	Alive	6/13/71		Alive	2/22/72
	Dead	7/16/71	B14MF	Killed	7/30/71
	Alive	9/10/71		Alive	10/19/71
	Alive	10/ 8/71		Dead	11/16/71
	Dead	11/ 5/71		Alive (?)	2/22/72
H28MF	Alive	7/13/71	B12HF	Found dead	9/ 2/71
	vanished (dead ?)	8/10/71		Alive	10/19/71
*H15CF	Alive	7/13/71		Dead	11/16/71
	vanished (dead ?)	8/10/71		Alive (?)	2/22/72
G 2HM	Found dead	3/10/71	*B 4CF	Found dead	9/12/71
	Alive	8/ 9/71		Alive	10/15/71
A15MM	Found dead	3/13/71		Dead	11/16/71
	Alive	5/ 3/71		Alive (?)	2/22/72
	Dead	6/ 1/71	E30LF	Found dead	1/22/72
	Alive	8/23/71		Alive	2/22/72
	Dead	9/20/71	*B15CF	Found dead	1/25/72
G16HM	Found dead	3/ 9/71		Alive	2/22/72
	Alive	8/ 9/71	C29HM	Found dead	3/29/71
	Dead	9/ 7/71		Alive	6/ 2/71
A 6HM	Found dead	2/25/71		Dead	6/30/71
	Alive	5/ 3/71	C12HM	Found dead	8/10/71
	Dead	6/ 1/71		Alive	10/20/71
	Alive	8/23/71		Dead	11/17/71
	Dead	9/20/71			
C23HM	Found dead	3/ 7/71			
	Alive	8/ 9/71			
	Dead	9/ 7/71			
E15MM	Found dead	1/21/72			
	Alive	2/25/72			
G 8MM	Found dead	9/ 3/71			
	Alive	11/29/71			
	Dead	12/27/71			

Senator BEALL. How does an animal vanish?

Senator KENNEDY. That is what I am trying to find out. Reincarnation—the secret has been found.

In a serious manner, what is this? What does this mean to you?

These are animals that are involved in different tests and studies on different tests. What is the significance of this kind of record-keeping which are supplied to the FDA?

Dr. SCHMIDT. The most reasonable explanation for this sort of finding is inadequate observation of animals in cages, perhaps inadequate marking of cages; but certainly a lax system of knowing the condition of each animal every day and reporting accurately that condition, and then carrying those figures through to the summary tables.

Senator KENNEDY. If you cannot get a person to tell whether the animal is dead or alive, what kind of value are you going to give to their analysis about whether it is a cancer-causing agent?

Dr. SCHMIDT. Generally, people can tell the difference if they look. The problem is often in not looking and knowing. This then results in animals that might be long dead, lying in the cage, and the subsequent problem of autolysis; that is, degeneration of tissues, so one cannot tell what he is looking at under a microscope.

Clearly, the meaning of this again is that one cannot rely as much as he would like, and in some instances not at all, on the results of the study.

We consider this, wherever it occurs, at Searle or in our own laboratories, which has happened occasionally, to be a serious, totally unacceptable practice.

Senator BEALL. Mr. Chairman, on that point it really has to be probably the result of inexperienced people observing these things; does it not? I just cannot believe that anybody who knows what they are doing cannot determine from day to day whether an animal is dead or alive. There must be some pretty easy test—

Dr. SCHMIDT. Having run laboratories myself, I can tell you that there are many problems. Most commonly, what happens is that the people one hires for animal keeping, or similar jobs, have little or no training. If little or no training is given to them, they do not understand what they are doing or what the significance is.

If there is no quality control operation in the laboratory to train the people and to see that they are doing what they are supposed to be doing, then one finds these kinds of circumstances that are really impossible to understand and explain. It just comes from a lack of running a proper laboratory.

Senator BEALL. Well, a laboratory that would show these kinds of results apparently would have no supervision whatsoever, would it?

Dr. SCHMIDT. If you look again, you will find sometimes longer periods of time go by. Supposing a study is going on and on Monday somebody records that the animal is dead and then that record sheet is taken away. Then on the next day, some other person comes and makes another observation, and this particular animal is reported on the record sheet as alive. These sheets could be accumulated for weeks or months, be set aside for a year and then one goes and looks at the raw data and says, "Good God, I cannot make any sense out of this." And then if he feels for whatever reasons he has to make some sense of it, then one gets summary sheets and so on that do not jibe with the raw data.

The error in the first place is in the observation of the animals and the construct of the raw data sheets. This is a very important point. I think, with regard to what one can or should do about the problem in correcting it. It says one must get at the observations and how they are made in the first instance.

Senator BEALL. It is interesting to note that one of these sheets, BIAMP, it says it was killed on July 30, 1971, and alive on October 19, 1971—apparently it was not an effective hit job.

Senator KENNEDY. Dr. Schmidt, we have just been talking about some of the drugs here, and I think for the purposes of our understanding of the problem, we should realize that it was not just on the drugs that you have mentioned, but on other drugs such as Norpace. The conclusions that you have reached on that, in the December 8 memo—on Point No. 4, it says:

Tissues reported to be examined do not correspond with actual data: for example, spinal cord (high dose and control) stated eight out of eight examined for each—actually zero out of eight examined. Mid-dose brains reported eight out of eight examined—actually zero out of eight examined. Parathyroid (control, mid- and high) eight out of eight reported examined—actual zero out of eight examined.

[The memorandum referred to follows in its entirety:]

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION

TO: Seale Investigation Steering Committee DATE: December 8, 1975

FROM: Seale Investigation Task Force

SUBJECT: Status Report on Investigation

Attached is material concerning the status of the investigation as of December 8, 1975.

Carlton Sharp
 Carlton Sharp

Addressees:

Dr. Alexander Schmidt
 Mr. Sherwin Gardner
 Mr. Sam Fine
 Mr. Paul Hile
 Dr. J. Richard Grout
 Mr. Richard Merrill
 Dr. Francis Eckley
 Dr. William D'Agostino
 Mr. Jerome Halperin
 Mr. Donald Martin
 Mr. Alvin Gottlieb
 Mr. Man in Shurette
 Mr. Carlton Sharp

Status of Searle Investigation

Completed Investigations - The investigations on 10 individual studies involving 7 different products have been completed by the investigating teams. Four final reports have been submitted to the Task Force. Three of the remaining six reports will be completed by December 10, 1975 and three by December 19, 1975 (See Appendix I).

Ongoing Investigations at Searle - There are six ongoing investigations involving five different products. Anticipated date of completion including submission of finished report is December 19, 1975, (See Appendix I).

Follow-up Investigations - A review of the final reports by the Lead Investigator and the Task Force may indicate the need for further follow-up at Searle, Hazleton, to ex-employees, etc. Currently, an investigation is scheduled at Microscopy for Biological Research, Ltd., (Mauro), Albany, New York, for the week of December 8, 1975, as a follow-up to the 78-week rat study on Aldactone done at Searle.

Changes in Investigational Plans

The following substitutions have been made in studies to be

Investigated:

<u>Original</u>	<u>Substitution</u>	<u>Reason</u>
SC 16895 (IND 5963) 26-week dog at Searle	Norpacc 40-week rat study	SC 16895 was subject of a discontinued IND (5963). After finding problems with the dog study on Norpacc, an active IND, we decided to use our limited resources on the active drug.
Silandrone Dog study, Hazleton Labs	Syncro-Mate 13-week dog study 13-week rat study Searle Labs	The Silandrone study was reported to the Task Force as done at Searle Labs and was so scheduled, but turned out to have been done at Hazleton. We chose Syncro-Mate because it was done at Searle by the same team that did original 80-week Flagyl study (McConnell, Martinez, and Sagartz).

Aspartame Pivotal Studies

Acting on a request from the Bureau of Foods (See Appendix 2) we placed the identified pivotal Aspartame studies under seal. This action was taken on December 3, 1975, within hours after the order was signed staying the approval of the food additive. (See Appendix 3 for list of studies under seal).

Conference between Task Force and Investigating Teams

A conference was held between the Task Force and the Investigating Teams on November 24 and 25, 1975. A summary of the more significant findings reported by the teams on each study is attached (See Appendix 4).

STATUS OF INDIVIDUAL INVESTIGATIONS

	PRODUCT	STUDY	FIRM	DATE REPORT COMPLETED OR DUE
I. Investigations completed with written reports	Aldactone Aspartame Norpace Cu7	104 week rat study	Hazleton	December 3, 1975
		104 week rat study	Hazleton	December 3, 1975
		52 week dog study	Searle	December 5, 1975
		52 week rat study	Searle	December 5, 1975
II. Investigations completed - Reports being written	Aldactone Flagyl Aspartame	78 week rat study	Searle	December 10, 1975
		Reproduction studies	Searle	December 10, 1975
		52 week monkey study	Searle	December 19, 1975
		52 week dog study	Searle	December 19, 1975
		46 week hamster study	Searle	December 19, 1975
		114 week rat study	Searle	December 19, 1975
III. Investigations ongoing	Flagyl Norpace Aspartame Ovulen Synro-Mate	80 week rat study	Searle	December 19, 1975
		40 week rat study	Searle	December 19, 1975
		Reproduction and teratology	Searle	December 19, 1975
		7 year dog study	Searle	December 19, 1975
		13 week dog study	Searle	December 19, 1975
		13 week rat study	Searle	December 19, 1975

MEMORANDUM

Appendix 2
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

TO : Carlton Shoup, RFD-330
Team Leader
G. D. Searls & Co. Investigation Team

DATE: December 2, 1975

FROM : Acting Director
Bureau of Foods, HFF-1

SUBJECT: Aspartame

The following studies are considered by our scientists to have been pivotal in the safety review of Aspartame (FAP 3A2885).

<u>Entry No. (FAMF 134)</u>	<u>Title</u>
E-11	Two Generation Reproduction Study in Rats of SC-18862 (Aspartame) PI 867871
E-23	106-Week Oral Toxicity Dog Study PI 855870 (of SC-18862 Aspartame)
E-22	52-Week Oral Toxicity Study in the Infant Monkey PI 856070 (of SC-18862 Aspartame)
E-33 (Appendix) & E-34	Two-Year Toxicity Study in the Rat PI 838871 (of SC-18862 Aspartame)
E-70	Lifetime Toxicity Study in the Rat PI 892872 (of SC-18862 Aspartame)
E-75	104-Week Toxicity Study in the Mouse (of SC-18862 Aspartame)
E-76	110-Week Toxicity Study in the Mouse PI 935H-73 (of SC-19192 Diketopiperazine)
E-77 & E-78	115-Week Oral Tumorigenicity Study in the Rat PI 933873 (of SC-19192 Diketopiperazine)

- 2 -

- E-86 A supplemental Study of Dog Brains from a 106-Week Oral Toxicity Study (PT 855S70) PT No. 1226 (cross-ref. E-28) (of SC-18862 Aspartame)
- E-87 A supplemental Study of Rat Brains from Two Tumorigenicity Studies (PT 838H71 & 892H72) (cross-ref. E34 & E70) (of SC-18862 Aspartame)

Other Studies of Interest re: Aspartame Petition

Entry No. (FAMF 134)Title

- A. E-27 46-Week Oral Hamsters Study PT 852S72
& E-35 (supplement) (of SC-18862 Aspartame)
& E-36 (supplement)
- B. Any one or two of a number of teratogenic/reproductive/Embryotoxic Potential Studies
Most recently submitted is E-89 & E-90.
- E-89 An Evaluation of Embryotoxic and Teratogenic Potential in the Mouse PT 1218 (of SC-18862 Aspartame)
- E-90 An Evaluation of Embryotoxic and Teratogenic Potential in the Rabbit PT 1201 (of SC-18862 Aspartame)
- C. Any one or two or a number of acute and short term oral toxicity studies of SC 18862 (Aspartame) or SC 19192 (Diketopiperazine)

We would appreciate the investigation teams' efforts in taking whatever steps are necessary to place all of the original information contained in these files under FDA control. As soon as this is completed, we will proceed to take whatever steps are necessary to determine the accuracy of the data submitted in the summaries which were reviewed by our scientists.

Howard R. Roberts
Howard R. Roberts, Ph.D.

PIVOTAL STUDIES ON ASPARTAME UNDER SEALAt Hazleton Laboratories:

1. Two Generation Reproduction Study in Rats of SC-18862 (Aspartame) PT 867 H 71
2. Two-year Toxicity Study in the Rat of SC-18862 (Aspartame) PT 833 H 71
3. Lifetime Toxicity Study in the Rat PT 692 H 72 (of SC-18862 Aspartame)
4. 104-week Toxicity Study in the Mouse PT 984 H 73 (of SC-18862 Aspartame)
5. 110-week Toxicity Study in the Mouse PT 985 H 73 (of SC-19192 Diketopterazine)
6. A Supplemental Study of Rat Brains from Two Tumorigenicity Studies (PT 839 H 71 and 892 H 72) of SC 18862 Aspartame
7. Toxicological Evaluation in the Neonatal Rat PT 893 H 71
8. Segment III Perinatal Weaning Study in the Rat PT 1011 H 72
9. Two Month Oral Administration in Rats. Final Report PT 719 H 69
10. Two Month Oral Toxicity in Dogs. Final Report PT 726 H 69

At Searle Laboratories:

1. 155-week Oral Toxicity Dog Study (of SC-18862 Aspartame) PT 855 S 70
2. 52-week Oral Toxicity Study in the Infant Monkey (of SC-18862) PT 855 of 70

3. 115-week Oral Tumorigenicity Study in the Rat
(of SC-19192 Diketopiperazine) PT 988 S 73
4. Acute Toxicity Studies in the Rat, Mouse, and
Rabbit (of SC 19192)
5. Acute Toxicity Studies in the Rat, Mouse, and
Rabbit of SC 18862
6. A Supplemental Study of Dog Brains from a 106-week
Oral Toxicity Study (PT 855 S 70) PT. No. 1226 (of
SC 18862 Aspartame)
7. 46-week Oral Hamster Study (of SC 18862 Aspartame)
PT 852 S 72
8. An Evaluation of Embryotoxic and Teratogenic
Potential in the Mouse (of SC 18862 Aspartame)
PT 1218
9. An Evaluation of Embryotoxic and Teratogenic
Potential in the Rabbit (of SC 18862 Aspartame) PT 1201
10. Two Week Oral Toxicity Study in the Mouse
PT 885 S 70
11. Two Week Oral Toxicity Study in the Rat
PT 884 S 70
12. Five Week Oral Toxicity Study in the Rat
PT 972 S 71

Significant FindingsMEB - 78 Week Rat Study - Searle Laboratories

- A. MEB, Ltd. (Mauro) Report - Delay in submitting "Alarming findings".
- B. Excision of tissue masses from live animals during course of study.
- C. Omission of malignant mammary tumors from statistical summary submitted to FDA.
- D. Inconsistencies in tissue mass regression entries.
- E. Presentation to Advisory committee - McCannell under-reporting of tumors in test group while over-reporting in controls.
- F. Errors in documents too numerous to count.

Albright - 104 Week Rat Study - Hazleton Laboratories

- A. Study design limits to 50% the number of animals fully evaluated microscopically in low and medium dose.

- B. Only 70% of the tissues projected for histological examination were actually examined, thereby reducing value of test in determining tumorigenicity.
- C. Histopathology report contains findings on many slides which according to laboratory's own records, were not made.

Aspartame - Searle Laboratories

- A. 52 Week Monkey Study
 - 1. False statements in submission concerning availability of animals for necropsy.
 - 2. Searle memo indicates "unexpected findings" and eye changes, but no mention of these in submission.
- B. 114 Week Rat Study - DKP
 - 1. 50% of the animals were fixed in toto. Report to FDA indicates prompt necropsy when in some cases it was more than a year from date of death.
 - 2. Excision of tissue mass in high dose female. Also skin incision over mass made in two (2) treated animals.

3. Changes in gross necropsy reports made by pathologist who was not present at necropsy.

C. 52 Week Dog Study

Report to FDA states all animals hearty - no diseases, but at least one animal was sick and treated during the study.

D. 46 Week Hamster Study

1. Animals fixed in toto - some not necropsied for a year or more.
2. Study discontinued because of "wet tail", (a disease of hamsters) but none of the symptoms of the disease are reflected in daily observation records.
3. At least in BUN's and Final Body Weights the firm could not confirm the means in the submission from their own raw data.

Aspartame - 104 Week Rat Study - Hazleton Laboratories

- A. Autolyzed tissues, with no observations, are included in the denominator of tissues examined for a calculation of the percent of toxic lesions present.

- B. At least four instances were noted where animals have unusual or usual lesions, but no slide was made. This is not in accordance with the protocol.
- C. Editing of Pathologist's Summary (not submitted to FDA) for final report which alters some of the pathologist's summarized findings.
- D. Tumors reported for 3 and possibly 5 treated animals for which no slides were found and no block cut.
- E. Positive findings report by pathologist on 15 sections for which no slides were ever made.

Aspartame Reproduction and Teratology Studies - Searle Labs.

Investigation of these studies has just begun. A document found by the investigating teams contains a statement by one of Searle's own consultants that, "He would not take much notice of very many of the studies because of bad experimental design, animal husbandry, and statistical analysis. He feels that the only useful study was the first dietary study which demonstrates impracticable to administer AFM in the diet".

Flagyl

A. 80 Week Rat Study - Searle Laboratories

1. Reports submitted to FDA in 1969, 1970, 1974, and 1975. Each contain variations on the number and/or kinds of tumors observed. The annotated version submitted in 1975 shows hundreds of corrections of the 1974 corrected version.
2. Gross necropsy records altered by a pathologist who was not present when gross necropsy was performed.
3. Pathology on at least 2 groups of animals (13 and 26 week sacrifice) was performed by two separate pathologists (McConnell and Sagartz) but only Sagartz's report was submitted to FDA.

B. Reproduction Studies - 3 Rat - 2 Rabbit - Searle Labs.

1. In one rabbit study, protocol called for 2% and 5% suspension, but 2% and 10% were reported to FDA, and 2% and 5% were actually given.
2. Delay in reporting studies to FDA, 4 years in one case and 6 years in another.

3. Questionable qualifications of senior investigator.

Norpace

A. 52 Week Dog Study - Searle Laboratories

1. Study submitted twice; once as part of an IND and later as part of NDA. NDA version shows numerous corrections of clerical (seemingly) errors in data.
2. FDA requests readings of low and mid-dose brains because of findings in high dose. Conclusion was reached that no changes observed in these groups, but this conclusion was based on a partial evaluation of only 3 of 16 brains and all 16 had artifacts on slides.
3. Drastic drop in blood levels of drug at week 40. Firm's records not adequate to determine whether or not the animals got the drug.
4. Tissues reported to be examined do not correspond with actual data: e.g. spinal cord (high dose and control) stated 8/8 examined for each -- actually 0/8 examined. Mid-dose brains reported 8/8 examined

-- actually 0/8 examined. Parathyroid (Control, mid, and high) 8/8 reported examined -- actual 0/8.

B. 40 Week Rat Study - Searle Laboratories

In progress, no report.

Cu7 52 Week Rat Study - Searle Laboratories

- A. Inadequate ante-mortem observations; e.g. animals reported in good condition were actually dead, inadequate reporting of tissue masses.
- B. Unreliable gross post-mortem observations on uterine polyps and tissue masses: e.g. polyp in slide but not reported on gross.
- C. Submission to FDA misleading in that implies that IUD (copper and plastic) was implanted but; in fact, there were three separate groups - sham operated, plastic, and copper. Reviewer has since been talked to and he assumed copper group had complete IUD implanted.
- D. Lack of professional supervision of prosectors. A memo of 10/31/71 from McConnell requested dating, initialing, and proofreading of the summary of ante-mortem observations

but this was not followed.

Ovulen - 7 Year Dog Study - Searle Labs.

- A. Original batches of tablets used during entire duration of 7 year study.
- B. 6th year interim report states that certain palpable mammary masses were transient. Raw data showed masses continuous throughout this period of the report.
- C. Enovid and Ovulen Dog Studies done in the same room at the same time.

Problems Common to Many Studies

1. Failure to assay product for potency or product-feed combination for homogeneity and stability.
2. No general program to determine absorption of chemical during study.
3. Ante-mortem observations are of questionable reliability.
4. Supervision and review of ante-mortem observations virtually non-existent.

5. Failure to use, initial, or date ante-mortem observation sheets.
6. Because of the perfunctory nature of the observations, tissue masses come and go and animals die more than once.
7. Animals not individually identified and feed cups not identified. Tals procedure conducive to error.
8. Lack of professional supervision of necropsy procedure.
9. Animals dying on study are fixed in toto and often not examined for up to 48 hr. Submission usually states animals examined promptly.
10. Necropsy reports submitted to FDA are frequently at variance with records.
11. Failure to check and verify raw data before submission to FDA (See attached reports on Flagyl and Aldactone). Emphasis appears to be on narrative report and conclusions submitted to FDA.
12. Long delay in preparation of final reports in Path-Tox department.
13. Unaccountable variations made by unidentified persons in both ante-mortem and post-mortem records.
14. Lack of adequate training and supervision of prospectors and

technicians.

15. General lack of knowledge of and control over status of a product by Searle personnel. Inability to verify or validate data in various phases of study from observation notes to submissions.
16. Apparent lack of firm direction, at the corporate level, of the Pathology-Toxicology Department and Regulatory Affairs Staff, to assure the credibility of studies and submissions to FDA.

Dr. SCHMIDT. Perhaps I could ask Dr. Gross to comment.

Senator KENNEDY. Well, just the fact that they have not been examined, is the principal point I was trying to bring here, not the details; and as I understand, that is part of your conclusions; is that correct?

Dr. SCHMIDT. Yes, sir.

I think that we found deficiencies and errors essentially in all of the 25 studies. What I have obviously attempted to do is illustrate some of them and to categorize some of them, as I mention later on in the statement.

There were some common findings in the various studies.

Senator KENNEDY. That is right.

We will obviously include this document in the record, but later it says—and these are overall conclusions for the drugs—

Because of the perfunctory nature of the observations, tissue masses come and go and animals die more than once. Necropsy reports submitted to FDA are frequently at variance with raw data. Unexplained alterations made by unidentified persons in both antemortem and postmortem records. Apparent lack of firm direction at the corporate level of the pathology-toxicology department and Regulatory Affairs staff to insure the credibility of studies and submissions to the FDA.

Those were general conclusions, as I understand, made with regard to the drugs that you reviewed.

OK. We will move ahead.

Dr. SCHMIDT. Perhaps I could move to the top of page 11 since I have been discussing in general these findings, and in all of the studies there were kinds of problems that can be characterized as I just did.

We have tried to step back from several specific deficiencies our investigators found to analyze the problems common to many of the studies reviewed at Searle, which were conducted from 1967 to 1975. These problems may be categorized as follows:

One: Technical personnel at Searle seem to lack an understanding of a number of aspects of their work;

Two: There appeared to be a lack of adequate control by Searle management over numerous aspects of the performance and analysis of animal studies; and

Three: Many decisions made in the course of designing, conducting, and reporting studies tended to minimize the chances of discovering toxicity and to allay possible FDA concern. I have illustrated, with numerous examples, these three categories of problems in my full statement for the record.

Senator KENNEDY. Before we leave that, talking about point No. 2, in listening to your statement, we are talking about not only management mistakes, but about scientific mistakes; are we not?

Dr. SCHMIDT. Yes; very much so.

Senator KENNEDY. That is of a major kind of importance. Other than just judgmental factors, different kinds of conclusions, we are talking about basic and fundamental mistakes in terms of scientific aspects of review?

Dr. SCHMIDT. Very much so. These really run the gamut of research work, from choosing and purchasing animals, through the de-

sign of a protocol, to the actual conduct of the study and the gathering and calculations of the data.

At each step, deficiencies have been found. I will judge scientifically that a majority of these were errors of omission in that there was a failure to do some good practice. And again I would tend to turn to the kinds of good practices that should be in these laboratories.

Senator KENNEDY. Mr. Commissioner, these points are important, but I think what is most important is the conclusions that you are going to draw from this report; what the implications are in terms of the safety and security of the American people, and what specifically the FDA is going to do about it, what you are going to do in terms of working with other agencies, that may very well have similar kinds of programs.

What we are very interested in is what any of us can do about it in terms of any kind of additional legislative authority or resources or whatever to try and provide some protection and permit you to do the job. I think after going over some of these matters this morning, anybody who has been listening or watching this exchange wants to know exactly what the nature of the real kind of threat is, what all of this means in terms of their own kind of safety and security, in terms of the general kind of work with the FDA, what you are going to do about it and what any of us can do, particularly here in the Congress, on it.

I think that would be a most important sort of summation, and we can put the rest of this in the record.

Dr. SCHMIDT. There are two principal questions. I think, to be addressed. You have already asked one: Are the problems found at Searle unique or industrywide? And, second, what do these findings have to say about the safety of our foods and drugs?

I have spoken to the first question. We are not now able to answer the first question definitely.

Senator KENNEDY. But you are going to take the steps to answer that?

Dr. SCHMIDT. I think we must assume, on the basis of the evidence the Agency has, that there is to some degree an industrywide problem. We are going to find out the extent and kind of problem that exists.

We have considered the second question—what does this mean in regard to the safety of the products on the market—very carefully during the last 6 months and in preparing for this hearing.

We believe that it clearly would not be responsible at this time to indict all past animal toxicology work because of what we have learned so far, or to single out particular drugs or food additives for special concern.

I would like to take just a moment to explain what may seem to be a somewhat more paradoxical reassurance. The scientific evaluation of drugs and food additives in this country involves a number of redundancies, checks and balances, safeguards, and fail-safe approaches. All of these serve to prevent a compound from being approved until it has been examined extensively and repeatedly by different observers, often in different laboratories, in multiple species, and against

a general background of scientific knowledge in pharmacology, toxicology, and drug metabolism.

This reassurance is based on the following considerations:

First of all, our regulations require that all animal studies conducted by drug sponsors be submitted for evaluation and that all studies containing "alarming findings" be submitted promptly.

Of course, if these regulations are violated, this then, at least partially, negates the value of those regulations and we must see to the regulations being followed.

Senator KENNEDY. They were violated here, were they not?

Dr. SCHMIDT. Yes; indeed they were. But we have numerous instances in which manufacturers have carried out their observations faithfully, even when the animal data they reported could or did have serious consequences for products of great commercial importance.

We do have many reports coming in of studies determining carcinogenicity and such, which is some reassurance.

Second, there is considerable redundancy in animal studies in that there are multiple studies of a single drug and studies of different drugs of a single class. There are numerous opportunities for discoveries to occur, even if an individual study is flawed by errors or carelessness.

The situation is similar with food additives. I might say, just as an aside, that this is one virtue of a highly complex and at times somewhat slow regulatory process that has been criticized recently in this country.

The primary data for approval of drugs come from clinical studies conducted in humans. Our system of drug development thus provides a large amount of information about the safety and effectiveness of drugs in humans, in addition to the information obtained in animals.

There are powerful economic and legal incentives for drug manufacturers to carry out proper animal studies of their products. Similar toxicological studies are done on closely related drugs by different drug firms, and competitors' products are not uncommonly included in such studies.

Animal toxicology is heavily concentrated in industry, and much professional interchange occurs among scientists in different firms. While any scientific discipline, like any other occupation, will have its share of careless individuals, an entire field of science is not likely to be incompetent or unethical. This professional integrity of toxicologists in industry helps assure the overall quality of animal investigations.

In summary, I would voice a cautious but responsible note of reassurance respecting the safety of foods and drugs now on the market, in spite of our findings to date. At the same time, our confidence must be somewhat diminished by our recent investigation. It is, therefore, essential that steps be taken to assure better performance.

In discussing what we think needs to happen, I would mention this under three separate headings----

Senator KENNEDY. Just before we do that, one of your points is that primary data for approval of drugs comes from clinical studies conducted in humans. We are going to be getting into that on Thursday.

What can you tell us about the reliability of that data? You have found in terms of animal data, one major company sufficient cause of alarm that you're going to take a total review, industrywide.

What can you tell us initially about the reliability of clinical studies conducted in humans?

Dr. SCHMIDT. There are several differences between the system of clinical research and this kind of animal research—

Senator KENNEDY. We find the system does not work too well, at least under present circumstances.

Dr. SCHMIDT. Clinical research is generally done in medical schools and places in which the research is done openly with peer review. Admittedly, the institutional review committees sometimes do not work well. There are, however, a number of checks and balances for human research that simply do not exist with the animal research.

Senator KENNEDY. Even with these checks and balances and even being done in medical schools, can you give us any assurance that that system is working very much better than the present system with regard to animals? It might be, it should be; but the question is: Is it?

Dr. SCHMIDT. You recall we testified on this at a previous hearing. We have looked more at clinical research, and I would believe it accurate to state that we have not found the kinds of very serious errors or the degree of errors in clinical research which we found in some of the animal toxicology research. There are things wrong clearly with both clinical research and the way we monitor that, and again we will be talking about that at another point. But there are not very serious kinds of discrepancies with clinical research.

Also, we require submission to the Agency of the raw data from clinical research; and we do not for the animal research. When we evaluate an NDA, we do so on the basis of some in-house review of the raw data.

Senator KENNEDY. We asked you about this in July, and I think you indicated to us that it may very well be a serious problem. In our July hearing, in a response to a question that I asked, and I would give you the citation but we just have the galley now:

As I mentioned earlier, this past month we had a number of investigations, examinations of IND's, NDA's, examination of certain research has been conducted. As I have indicated to you, Mr. Chairman, and your staff, I have become increasingly alarmed and upset on what we have discovered.

And then I said:

There is serious observation you have made in testimony about much of the clinical work on jobs done in this country, seriously flawed because of inattention or proper planning or conduct of the study or lack of skill on the part of the investigator.

We are going to develop that point during the course of later testimony. This is a considerable concern.

So is there anything that has happened since July to relieve you of that concern?

Dr. SCHMIDT. No; that concern remains; and I would certainly repeat what I said previously about clinical research. I think what I am trying to do here is draw a distinction in degree between some of the things that we have determined in the Searle investigation and

what we have determined are the deficiencies in clinical investigation. I do not think that some of the abysmal findings observed with the animal work have been observed with the clinical research. Some of them are the same. Faults in protocol design can be found in both clinical research and animal research. Inadequate training of research workers is to be found in both, and sometimes improper data handling is to be found both in clinical research and animal toxicology research. Some of the other things are not common to each and, in general, clinical research is done in a much more open fashion.

There is no trade secret problem as we have discussed many times. There is not the problem with one firm doing all of the work. Clinical research is very often published in open medical literature, and so on.

I think there are differences in deficiencies, certainly, in degree and on occasion in kind between the two systems of research.

We do get the raw data in-house on clinical research.

Senator KENNEDY. Do you want to summarize the last part of your testimony? I think you have covered most of it.

Dr. SCHMIDT. We are going to proceed with the Searle investigation, as I said, to conclude it promptly and make decisions as to what the next steps might be, including the decision about the urgency of further auditing of additional Searle drugs as compared with the necessity for auditing on a more broad front the performance of the entire industry.

But we will design and are designing a sampling system for the industry at large, and we will proceed with that system as our resources and our very tired investigators will allow.

The final decisions about how many firms we are going to inspect, how many studies and so on, will await my determination of the outcome, within the next several weeks, of this Searle investigation; and then I will be in communication with you about our next steps.

I think a serious consideration is the larger question of what changes need to be made in this system of animal toxicology research to assure that studies are of high quality and are entirely reliable. We have carefully considered a number of alternatives, and again in my full testimony we have explored at some length various alternatives that have been suggested to us by others, other Federal agencies and by our own staff. But we have rejected some of them as too costly, too difficult to implement, or both. These included such strategies as Federal or third-party conduct of research; continuous on-site monitoring of research by the Government; and the submission and review of all raw-animal data.

A discussion of these alternatives, including our reasons for not adopting them is contained in my longer statement.

We are recommending the following approach:

First, we—and by “we,” I mean the Federal Government—establish by regulation animal-testing standards to be known as good laboratory practice regulations, (GLP’s), analogous to our good manufacturing practice regulations, (GMP’s) and require the establishment in pharmaceutical houses, or other people who do or contract our research, quality control units who would monitor the performance of this research and how it is done.

Second, we must establish a systematic auditing program under which FDA investigators would inspect all animal testing facilities at least annually to determine whether they were operating in compliance with GLP regulations and to audit the records of the quality-control unit to establish whether or not it was performing its job as internal monitor.

We must continue to conduct, on an ad hoc basis, indepth retrospective review of raw data when there is suspicion of falsification or serious error. But this approach is enormously costly in resources, as the Searle investigation has shown, and cannot be routine.

The sanction employed when poorly conducted studies are discovered should ordinarily be rejection of the studies for any decision-making purpose. Because of the cost of research, denial of approval is, in fact, an extremely heavy penalty.

Finally, one of the possibilities we intend to discuss with other agencies in our planning for the future is the feasibility of certification of animal testing laboratories by the Federal Government.

I would add that on January 15, 1976, we met with representatives of the Environmental Protection Agency and the National Cancer Institute [NCI] to discuss our mutual concerns in this area. We have agreed to cooperate in gathering additional inspectional information on the performance of toxicology laboratories in this country.

Our first step in this will be to exchange information about the numbers and kinds of laboratories, to identify the university that I mentioned conducts these studies. In addition, we have agreed to collaborate in drafting any necessary new regulations and to include other Federal agencies in these decisions.

As some in this room know, I have talked about officials of HEW and independent agencies; and I can say that everyone is anxious to contribute to a program that would solve the problems that we have identified in our investigations.

In summary, Mr. Chairman, members of the committee, we are well aware that we must pursue the program I have described—promptly and vigorously. The need has been made clear by the investigations I have reported this morning. We must have an effective quality-control system for laboratories engaged in the important work of assuring the safety of chemicals introduced into our society, wherever and however they are introduced, including drugs, food additives, pesticides, and the many other kinds of chemicals that are pervading our environment today.

I pledge we will respond to your earlier stated challenge to move ahead quickly and vigorously and to keep everyone, including the public, informed as to the steps we are taking that will accomplish our goal.

I appreciate being able to go through this statement, Mr. Chairman.

Senator BEALL. Dr. Schmidt, you have indicated this morning that in the case of Searle, at least questionable practices have existed and research of dubious professional competence has been produced; that this may or may not be a condition that exists throughout the industry.

Can you assure us these same conditions do not exist in the public laboratories that may be operating around the country, performing animal toxicology experimentation and research?

Dr. SCHMIDT. No, indeed. I cannot, with one possible exception. I think that what we have illustrated very graphically is the lack of and the need for detailed, explicit, written practices for laboratories, practices which would prevent this kind of thing from happening. These do not exist—

Senator BEALL. Public and private?

Dr. SCHMIDT. Public and private.

I am familiar with laboratories in medical schools. I am certainly familiar with our own laboratories. Again, as many people know, we were highly embarrassed by a study that we performed in our own laboratories. We had a mixup of two groups of animals getting a test substance. One of the fascinating things that FDA is doing is supporting the National Center for Toxicological Research [NCTR]; and one of the things being done there is an examination of the systems for doing this kind of research, which systems would actually be fail safe. NCTR has gone a long way in this regard. Dr. Cranmer, Director of that Center, has consulted frequently with NCI, who is implementing procedures that do upgrade the conduct of this kind of research. We do know enough to know that there are practices which, if followed, would go a long way toward guaranteeing the integrity and the value of this research. We just have to put these in place and be sure that they are followed.

Senator BEALL. It would seem to me in this instance the scientific community ought to be upset about this. Is there not peer review within the scientific research community that would cause the whole body of people doing this kind of work to be concerned about what one group may be doing one place that reflects on the professional competence of the profession?

Dr. SCHMIDT. I would point out two problems with that construct for animal toxicology research. First is that much of this research is done in-house as a kind of commercial secret, so that the peer review, the public examination of these kinds of studies does not occur.

Second, if it does occur, it occurs way late many times. So there is not the interest in it, and so on, that there is in, say, a clinical study reported in the New England Journal of Medicine, where everybody is hot to find out whether it can be reproduced, and so on.

The kinds of public control that exist in open research frequently do not exist with animal toxicology research because of trade secret problems, in-house problems, and the types of research that are involved in animal toxicology.

One of the problems with research is that research that is not fashionable often does not draw the attention of journal editors, prize givers, and the people who admit people to prestigious societies, and so on; so this research is not examined with the interest and frequency that other kinds of research is.

Senator KENNEDY. All right.

[The prepared and summary statements of Dr. Schmidt follows:]

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STATEMENT

BY

ALEXANDER M. SCHMIDT, M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON LABOR AND PUBLIC WELFARE

AND

SUBCOMMITTEE ON ADMINISTRATIVE
PRACTICE AND PROCEDURE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

JANUARY 20, 1976

- 1 -

Mr. Chairman and Members of the Subcommittees:

We are here this morning to present the Food and Drug Administration's views on the quality of animal testing being conducted on the products we regulate under the Federal Food, Drug, and Cosmetic Act, and on our investigation of Searle Laboratories in this regard.

ROLE OF INDUSTRY

Let me begin by emphasizing that under the Federal Food, Drug, and Cosmetic Act, manufacturers carry the burden of demonstrating that their products meet the safety standards of the law. The Food and Drug Administration (FDA) does relatively little toxicology testing of its own and no clinical testing. Instead, we set requirements--that is, state the type and extent of testing we believe is necessary for a determination of safety--and then review the data submitted by manufacturers to determine whether they meet these requirements.

FDA REQUIREMENTS

As an example, we require that all new drugs, food additives, or potentially toxic residues undergo extensive testing in animals to determine whether they have any teratogenic potential--that is, whether they can produce deformed offspring in animals. Similarly, we require long-term testing of these agents in animals for potential carcinogenicity whenever there is the likelihood of chronic exposure

of humans to such chemicals. In addition, a host of other toxicology studies are performed, in which several different species of animals are exposed to widely differing doses of the compound for periods of time ranging from a few days to many months, or even years.

PURPOSE OF ANIMAL STUDIES

Animal studies of human drugs are of particular importance in determining whether new products can safely be tested in humans to assess their potential therapeutic effect. The results of such studies alert investigators to possible adverse effects, aid in planning the dosages which should properly be studied in humans, and guide the designing of trials to evaluate the safety and effectiveness of the drug in human use. Animal studies are also of great importance in determining whether a drug has potential teratogenic effects or serious long-term effects such as carcinogenesis.

Similarly, with respect to food additives and chemical residues, including pesticide residues and environmental contaminants, animal testing is also particularly important in assessing the potential for teratogenic effects or serious long-term effects, including carcinogenesis. Such testing cannot feasibly be conducted in humans. Thus animal data are paramount for a determination of safety of these chemicals.

NEED FOR SOUND PROTOCOLS AND QUALITY CONTROL

Because of the importance of animal toxicology data to decisions regarding the safety of drugs, food additives, chemical residues, and

environmental contaminants, it is essential that these studies be conducted according to scientifically sound protocols and with detailed attention to their quality control. Major toxicological studies are technically complex, often involving hundreds of animals taking different doses of the test chemical for months or years, with each animal subject to repeated observations on growth rate, nutritional status, appearance, behavior, blood chemistry values, and the development of gross or microscopic lesions in the various organs of the body. Such studies cannot be conducted without the combined efforts of toxicologists, pathologists, statisticians, animal husbandry experts, and technical personnel.

QUALITY CONTROL PROBLEMS

Regretably, I must report that the required attention to detail in conducting these studies is sometimes lacking. For some time the FDA has been concerned about the absence of industrywide standards for the conduct of animal studies. The importance and complexity of these studies are by themselves sufficient reasons to recommend such a program. But, in addition, there is now growing evidence of significant quality control problems in these laboratories. Some of this evidence comes from the Searle investigation and some from other investigations conducted by the Agency.

My purpose today is to review the experience of the FDA in this area and, on the basis of this experience, to outline the approach the FDA intends to take to improve the way manufacturers carry out their

studies and the way we monitor their performance. As we testified before your Subcommittees on July 10, 1975, complete and accurate data are essential to rational decisionmaking by both the industry and the FDA. There can be no compromise in our insistence on accurate scientific data. That is a fundamental principle of both law and medicine.

RECENT HISTORY OF FDA INVESTIGATIONS OF ANIMAL LABORATORIES

On one well-publicized occasion, we discovered that animal data were improperly withheld or falsified. In 1962, Richardson-Merrell Laboratories were in possession of dog and rat data on Mer-29, a drug intended to reduce serum cholesterol which, had the data been submitted in accurate form in the new drug application (NDA), would have led to an earlier recognition of the drug's capacity to cause cataracts and certainly would have affected the drug's marketing status.

In 1965 plans were developed by the Division of Toxicological Evaluation of the then Bureau of Scientific Standards and Evaluation for a survey to determine how well animal studies were conducted and the data from them recorded and transmitted.

Records are available concerning at least one visit conducted under the 1965 program. The program was disrupted by a reorganization in mid-1966 that placed the reviewing pharmacologists of the Division of Toxicological Evaluation into the various divisions of the then Bureau of Medicine.

In 1969, new plans were developed for site visits to laboratories conducting animal studies to be conducted by the supervisory pharmacologist and staff pharmacologists from each of the six reviewing divisions of the Office of New Drugs and the Office of Marketed Drugs.

A few site visits were conducted under this program, and in FY 1971 an expanded program was developed. This program was more directly related to regulatory action, and coverage was broadened by utilization of field resources. The Scientific Investigations Staff, which until then had inspected only clinical investigators, was augmented by a pharmacologist, and a program was developed with the cooperation of the Office of Compliance and the Executive Director for Regional Operations for conducting both routine inspections and for-cause visits to laboratories whose reports had raised questions.

A number of the investigations carried out under this program were discussed at the July 1975 hearings. These investigations indicated that important information derived from animal studies was sometimes reported late, or apparently withheld from the FDA. As a consequence, the Bureau of Drugs has drafted proposed regulations to ensure prompt and timely reporting of animal safety studies.

TESTIMONY AT JULY 10, 1975 HEARING

At the July 10, 1975 hearing of the Subcommittees, we described the questions that had arisen regarding the integrity of animal data submitted to the Food and Drug Administration (FDA) in support of

safety of drugs. Specifically, we presented evidence arising from inspections of the G. D. Searle Company which reviewed studies on Flagyl and on Aldactone.

Flagyl had been approved for short-term treatment of trichomoniasis. When the firm sought to investigate this drug for a condition requiring prolonged administration, it was asked to perform long-term animal studies. Review of these studies found discrepancies between individual animal findings and summary tabulations, and a resubmission intended to clarify the matter appeared rather to confound it further. It was therefore decided that an inspection by our scientists of the raw data at the firm was in order.

While this investigation was in progress, the second drug, Aldactone, was undergoing review for presentation to an advisory committee because animal studies reported to us in March 1975, suggested that it was an animal carcinogen. Our review of the Aldactone studies also revealed a number of deficiencies and discrepancies in the tabulation and analyses of the data by the firm. As a consequence, our analysis and conclusions were quite different from the presentation made by representatives of the firm before the advisory committee in June 1975.

In an attempt to determine the circumstances under which the deficiencies and discrepancies occurred, Drs. Frances Kelsey and Adrian Gross visited Searle shortly after the advisory committee meeting.

From these preliminary investigations we concluded that an indepth study of the experimental animal operations of the firm was very much in order and, as you recall, we agreed at the hearing of July 10, 1975 to investigate the animal studies submitted in support of Searle drugs marketed since 1968. Subsequently, we decided to include in the investigation additional submissions from Searle, including the investigational drug Norpace and the food additive Aspartame.

SEARLE INVESTIGATION

To conduct the investigation of animal studies at Searle efficiently and expeditiously a Task Force was created composed of representatives of the Bureau of Drugs, Office of the General Counsel, Associate Commissioner for Compliance, and the Executive Director for Regional Operations. The Task Force is chaired by Mr. Carlton Sharp, a Compliance Officer in the Bureau of Drugs, who has been given complete authority to assign investigational activities to FDA personnel.

The Task Force was charged:

1. To review the practices of the G.D. Searle Company in conducting animal experiments, in analyzing the data from these experiments, and in submitting this information to the FDA;
2. To determine if there is evidence that any practices of Searle in conducting the above activities are in violation of the FD&C Act or any other laws of the United States; and

3. To recommend an appropriate course of action based upon the findings of the investigation.

The Task Force reports to a Steering Committee composed of the Commissioner, the Deputy Commissioner, the Associate Commissioner for Compliance, the Director of the Bureau of Drugs, the Executive Director for Regional Operations, and the General Counsel for FDA. The Steering Committee oversees the progress of the investigation and serves as a deciding body for major issues of policy and investigative strategy. A copy of my memorandum of July 23, 1975, which established the investigation Task Force and Steering Committee will be submitted for the record.

PLAN FOR INVESTIGATION

The Task Force began work in August 1975 and promptly prepared a plan for the investigation which called for:

1. Identification of Searle animal studies submitted to the FDA since January 1, 1968;
2. Development of criteria for the selection of products and studies to be reviewed and investigated;
3. Selection and orientation of headquarters and field personnel required to conduct the investigation; and,
4. Establishment of mechanisms for the actual conduct of the investigation at Searle and contractor laboratories.

The investigative plan will also be submitted for the record.

Because the investigation involved a mixture of law enforcement and scientific problems, the Task Force recommended the formation of teams to investigate the individual studies, each composed of two specially qualified drug investigators from various District offices of FDA and one or two pharmacologists from the Bureau of Drugs and Bureau of Foods.

Mr. Philip Brodsky, one of FDA's most experienced drug investigators, was selected as the lead investigator to direct all field aspects of the investigation and report directly to the Task Force. In order to provide expert scientific consultation to the Task Force and to the field investigators, Dr. William D'Aguanno, Assistant Associate Director for New Drug Evaluation (Pharmacology-Toxicology), was assigned to work with the Task Force on a full-time basis.

Dr. Adrian Gross of the Scientific Investigations Staff was assigned to provide full-time consultation in pathology and statistics to the field investigative teams and to work directly with the lead investigator at the Searle plant. Dr. William Fairweather, a statistician in the Division of Biometrics, was assigned to review statistical procedures used by the firm as well as to consult with the investigational teams.

Initially the investigation had been planned for four teams at Searle, each consisting of two investigators and one pharmacologist. It was noted, however, that a large number of studies submitted in support of Searle products had been conducted by the Hazleton Laboratories in Falls Church, Virginia. In late September,

the number of teams was expanded to six so that simultaneous investigation could be undertaken of studies conducted by Searle at its Laboratories in Skokie, Illinois and by the Hazleton Laboratories in Virginia.

Review of Searle Submissions

As a first step, each of the new drug evaluation divisions of the Bureau of Drugs and the Division of Toxicology of the Bureau of Foods reviewed all Searle submissions of animal data since July 1, 1968, to identify the laboratory which performed the study, the purpose of the study (reproductive, metabolic, chronic, acute, etc.), the animal species involved, the duration of the study, and the route of administration of the product. Included in this review were submissions on new studies of Aidactone and Flagyl, the drugs which had been discussed in the July 1975 hearings; interim reports on a long-term study of Ovulen, an oral contraceptive, and studies on CU-7, an intrauterine device, both of which are marketed; Aspartame, an approved food additive the firm had voluntarily withheld from marketing pending a hearing to review safety questions raised by public objectors; Norpace, a cardiovascular drug for which there is a pending new drug application; and Syncro-Mate, a veterinary drug.

Selection Criteria

The Task Force then established criteria for selecting the products and the specific studies to be investigated intensively. The highest priority products were identified as those which involved the greatest number of person-years of exposure; food additives were placed ahead of drugs. The selection criteria are presented as Appendix A.

