MEMORANDUM

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

TO : Searle Investigation Steering Committee

DATE: MAR 2 4 1976

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FROM : Searle Investigation Task Force

SUBJECT: Final Report of Investigation of G. D. Searle Company

This memorandum forwards the final report of the Searle Investigation Task Force on the practices of G. D. Searle Company in conducting animal experiments. The Task Force has selected only those findings for inclusion which it feels to be among the most significant or most representative of the findings noted throughout the individual study investigations. The investigation reports and their associated exhibits are available from the Task Force for reference; they are too voluminous to include here.

In addition to a description of some of our findings in the investigation, the report includes a section of recommendations for appropriate follow-up actions. Further actions resulting from this investigation should be processed through normal Agency channels.

With acceptance of this report by the Steering Committee, the Task Force has completed its mission and should be disbanded.

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SEARLE INVESTIGATION TASK FORCE

REPORT OF

PRECLINICAL (ANIMAL) STUDIES

OF

G. D. SEARLE COMPANY

SKOKIE, ILLINOIS

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Summary and Conclusions

At the heart of FDA's regulatory process is its ability to rely upon the integrity of the basic safety data submitted by sponsors of regulated products. Our investigation clearly demonstrates that, in the G. D. Searle Company, we have no basis for such reliance now.

Reliance on a sponsor is justified when FDA has reasonable assurance that the sponsor will: (1) inform the agency of all material results, observations, and conclusions of an experiment, (2) report fully and completely all of the conditions and circumstances under which an experiment was conducted, and (3) submit its reports to FDA in a timely fashion so that measures to protect the public health and safety can be taken promptly when warranted. Through our efforts, we have uncovered serious deficiences in Searle's operations and practices which undermine the basis for reliance on Searle's integrity in conducting high quality animal research to accurately determine or characterize the toxic potential of its products.

Searle has not met the above criteria on a number of occasions and in a number of ways. We have noted that Searle has not submitted all the facts of experiments to FDA, retaining unto itself the unpermitted option of filtering, interpreting, and not submitting information which we would consider material to the safety evaluation of the product. Some of our findings suggest an attitude of disregard for

FDA's mission of protection of the public health by selectively reporting the results of studies in a manner which allays the concerns of questions of an FDA reviewer. Finally, we have found instances of irrelevant or unproductive animal research where experiments have been poorly conceived, carelessly executed, or inaccurately analyzed or reported.

While a single discrepancy, error, or inconsistency in any given study may not be significant in and of itself, the cumulative findings of problems within and across the studies we investigated reveal a pattern of conduct which compromises the scientific integrity of the studies. We have attempted to analyze and characterize the problems and to determine why they are so pervasive in the studies we investigated.

Unreliability in Searle's animal research does not imply, however, that its animal studies have provided no useful information on the safety of its products. Poorly controlled experiments containing random errors blur the differences between treated and control animals and increase the difficulty of discriminating between the two populations to detect a product induced effect. A positive finding of toxicity in the test animals in a poorly controlled study provides a reasonable lower bound on the true toxicity of the substance. The agency must be free to conclude that the results from such a study, while admittedly imprecise as to incidence or severity of the untoward effect, cannot be overlooked in arriving at a decision concerning the toxic potential of the product.

We conclude the following:

1. There is disregard by Searle technical personnel of a number of important aspects of their work including: (a) the significance of the studies which they were conducting; (b) the need to adhere assidiously to research protocols; (c) the need to make accurate observations of the appropriate parameters and to document these observations promptly, adequately, and accurately and to sign and date the records of their observations; (d) the need to assure the accuracy of data which are transcribed from original documents to final reports; (e) the need to assure proper and accurate administration of the product under test; and (f) the need to observe proper laboratory, animal husbandry, and data management procedures.

2. There is disregard of the concept of adequate evaluation and control by Searle management over numerous aspects of the performance and analysis of animal research including: (a) activities and critical decisions of the Pathology-Toxicology Department; (b) supervision and continuity of personnel responsible to assure the quality of research and to provide continuity of knowledge and identification of problems of Searle products; (c) assurance of the scientific qualifications and training of personnel involved in the conduct of research; (d) verification

of the accuracy and completeness of scientific data in reports of preclinical research in a systematic manner prior to submission to FDA; and (e) failure to adequately monitor the studies performed in whole or in part for Searle by contract laboratories.

3. Searle made a number of deliberate decisions which seemingly were calculated to minimize the chances of discovering toxicity and/or to allay FDA concern, including:

designing protocols which call for fewer animals to be examined histopathologically in certain groups than were available;

using fixation in-toto with necropsy at a later date, possibly resulting in greater loss of tissues to autolysis;

excising tissue masses from live animals, in some cases without histologic examination of the masses, in others without reporting them to FDA;

selecting statistical procedures which used a total number of animals as the denominator when only a

portion of the animals were examined, thus reducing the significance of adverse effects;

using autolyzed tissues in the denominator of calculations for determining the number of toxic lesions noted in the study;

presenting information to FDA in a manner likely to obscure problems, such as editing the report of a consulting pathologist or including important data in individual animal records, and not highlighting the importance of the data in the summary;

delaying the reporting of alarming findings;

reporting one pathology report while failing to submit, or make reference to another, usually more adverse, pathology report on the same slide;

reporting animals as unavailable for necropsy when, in fact, records indicate that the animals were available but Searle chose not to purchase them.

4. In addition, Searle made other decisions which may have been inadvertent or unintentional which produced similar results, including:

too few data were collected or data were lost;

tissue masses reported in antemortem observations, as late as the day of necropsy, which were not reported at necropsy;

tissue masses or tumors reported at necropsy for which slides were not made or were not read;

clerical or arithmetic errors which resulted in reports of fewer tumors.

5. Although our investigation did not include an equal number of studies done by Searle's contractor, Hazleton Laboratories, the two studies done by Hazleton which we did review demonstrated some of the same problems found at Searle, i.e., large numbers of autolyzed tissues, failure to assay test substance; failure to assay treatment-diet mixture; failure to adequately review records and verify their accuracy; the use of statistical methods which included autolzyed tissues,

on which no observation had been made, in the denominator for determining the number of lesions found; lesions reported at necropsy for which slides had not been made; tumors reported microscopically for which slides had never been made.

Having reviewed the practices regarding animal experiments at Searle, we find that many of the problems are the result of lack of quality assurance. The results were and are so serious in some studies as to make it difficult, if not impossible, to draw conclusions regarding the full toxic potential of the products from the data. Without adequate control of every step of a study, one cannot assess the adequacy of the results if they are not indicative for toxicity.

Further, in response to the Commissioner's charge to determine whether there is evidence that any practices of Searle were in violation of law, our investigation has developed evidence of such violations.

Searle Task Force Recommendations

Recommendation #1 - Administrative actions on Searle products:

This investigation raises serious questions regarding the reliability and the scientific integrity of the studies submitted in support of the products we investigated. We recommend that the Task Force Report, together with the inspection reports and their exhibits covering the individual studies, be referred to the appropriate Bureaus. The Bureaus should determine whether some administrative and/or regulatory action is indicated with respect to these studies and products, as well as Searle products not the subject of this investigation.

Additionally, the Bureau of Foods should make a determination on the disposition of the Aspartame studies currently under official FDA seal at Searle and Hazleton Laboratories.

The Task Force Report should be referred to the Bureau of Biologics, the Bureau of Medical Devices and Diagnostic Products and the Bureau of Radiological Health to determine whether the findings noted are suggestive of problems associated with products under their jurisdiction.

Recommendation #2 - Acceptability of Animal Study Submissions to FDA:

We recommend that the consideration be given to regulations or legislation that would permit FDA to impose sufficient sanctions against laboratories or firms which submit animal studies produced under conditions such as we have found in this investigation so that FDA can be assured of the scientific quality of animal studies submitted to it in the future.

Recommendation #3 - Administrative follow-up at Hazleton Laboratories:

We recommend further investigation of Hazleton Laboratories to determine its methods of conducting, analyzing, and reporting research on animal studies.

Recommendation #4 - Other Firms and Private Consulting Laboratories:

FDA should proceed with its current plan to investigate animal research conducted by other companies, private testing laboratories and university laboratories in support of submissions to FDA to determine whether or not similar problems to those found at Searle exist industry-wide.

Recommendation #5 - Good Laboratory Practice Regulations:

The Food and Drug Administration should establish "Good Laboratory Practice Regulations" (GLP's) analogous to the drug current good manufacturing practice regulations (GMP's).

Further, FDA should enforce the same standards for animal research conducted in foreign countries submitted to FDA.

Recommendation #6 - Legal Action Against the G. D. Searle Company:

We believe sufficient evidence has been developed to warrant further investigation by the appropriate units within FDA with a view to regulatory action where indicated. In addition, we recommend that FDA recommend to the Department of Justice that grand jury proceedings be instituted in the Northern District of Illinois utilizing compulsory process in order to identify more particularly the nature of violations and to identify all those responsible for such violations.

ıction and Purpose of Investigation

ıvestigation of G. D. Searle Company was initiated by the Commissioner gh his memorandum of July 23, 1975 (Attachment 1) entitled: "Estabnent of a Searle Investigation Task Force and Steering Committee." memorandum states:

"Recent investigations by the Agency have raised questions about Searle Laboratory's conduct of animal experiments and thei: reporting of data to the Food and Drug Administration. Because of the importance and sensitivity of this investigation, I am hereby appointing a 'Searle Investigation Task Force' and a 'Searle Investigation Steering Committee.' The purpose of these groups is to assure that the investigation proceeds in a timely and effective manner, and that it receives high priority attention from the several units of the Agency involved in the investigation."

The charge to the Task Force was:

1. To review the practices of Searle Laboratories in conducting animal experiments, in analyzing the data from these experiments, and in submitting this information to the Food and Drug Administration.

2. To determine whether there is evidence that any practices of Searle in conducting the above activities are in violation of the Food, Drug, and Cosmetic Act or any other laws of the United States.

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

The Task Force was composed of representatives of the Bureau of Drugs, Executive Director for Regional Operations, Associate Commissioner for Compliance, and Office of the General Counsel. It reported to a Steering Committee composed of the Commissioner, Deputy Commissioner, Associate Commissioner for Compliance, Director, Bureau of Drugs, Executive Director for Regional Operations, and General Counsel for FDA. The Steering Committee was responsible to oversee the progress of the investigation and to serve as a deciding body for major issues of policy and investigative strategy.

of Investigation

s of the investigation of Searle Laboratories dates to 1970 when submitted its results of an 80 week toxicity study of metronidagyl) in rats to FDA. Flagyl had been approved for short term t of trichomoniasis in 1963. When Searle amended its IND to ine this drug for a condition requiring prolonged administration, n was requested to perform long term animal studies. Searle conthe 80 week rat study which was reviewed in the Division of Antiive Drug Products.

quent to the Division's review, the agency became aware of a study ice conducted by an independent investigator which contained positive ence of carcinogenicity. This prompted FDA to re-examine the data nitted by Searle of its 80 week rat study.

on reevaluation of these data in 1972, the Division of Anti-Infective ug Products requested consultation in pathology and statistics from r. M. Adrian Gross, then Associate Director of the Office of Pharmaceuical Research and Testing. Dr. Gross noted discrepancies between the summaries of the study and individual animal data sheets. From his analysis of data from individual animal data sheets, Dr. Gross concluded that there was a positive carcinogenic effect of Flagyl in the rat.

A meeting was held with Searle representatives in May 1972, at which they were advised of Dr. Gross' analysis, conclusions and findings regarding discrepancies in the firm's report of the study. The firm was asked to clarify the discrepancies. Searle submitted two chronic studies of Flagyl in mice and the "corrected" report of the 80 week rat study in April 1974, two years after the firm was advised of the discrepancies in the report of the 80 week rat study. Dr. Gross reviewed the entire submission relating to animal studies and concluded that the Flagyl mouse studies showed a positive carcinogenic effect. He also reviewed the "corrected" 80 week rat study. He noted that among the "corrections" made in the 80 week study, was a change regarding the report on rat CM-21. In the original submission of 1970, this animal was noted in a histopathology summary as having an adenocarcinoma of the mammary gland while the individual animal data sheet indicated a fibroadenoma of the mammary gland. Dr. Gross noted that the "corrections" were made not to the summary of the report, but to the individual data sheet for that animal. This was considered to be highly unusual as summaries are generally made from the individual animal records. FDA concern over the nature of this "correction" resulted in a "for-cause" inspection of this study at Searle. Because of their familiarity with these data, Dr. Gross and Mr. John Davitt, Supervisory Pharmacologist of the Division of Anti-Infective Drug Products, were assigned to conduct the investigation with a field investigator in May 1974. Dr. Gross and Mr. Davitt were unsuccessful in their attempt to do a thorough review of the raw data of this study because of Searle's failure to provide certain material which they requested. As a result, further

investigations were conducted by FDA's Chicago District Office, whose investigators also could not complete their investigation because of an inability to obtain various important documents from this study. Their investigation was terminated in May 1975.

Concurrently with the investigations of Flagyl, FDA was advised by Searle of a preliminary evaluation of a study of spironolactone (Aldactone^{R}) administered to rats, which indicated a positive tumorigenic effect. The study was further evaluated by Searle and submitted to FDA in March 1975. In the review of these data by FDA, discrepancies were noted between summary tables, statistical analyses and the individual animal data sheets with relation to certain histopathological findings. Among the discrepancies in the statistical summary submitted to the FDA was the failure to report the existence of malignant mammary tumors, although such findings were noted in the individual animal histopathology sheets. A determination was made at that time to investigate the reasons for these differences and omissions.

At a meeting of FDA's Cardio-Renal Drug Advisory Committee on June 10, 1975, presentations made by Searle representatives and FDA personnel differed in the evaluation and conclusions of the tumorigenic and carcinogenic potential of Aldactone. This difference was of concern to the Advisory Committee and to FDA.

On July 1 and 2, 1975, Drs. Frances O. Kelsey and M. Adrian Gross visited Searle Laboratories in an attempt to determine the reason for the omission of these malignant tumors and other discrepancies noted in the data. They were told by Searle representatives that the reason for the discrepancies was an error by a clerk in the Mathematics-Statistics Department who had been charged with tabulating the data and entering them into a computer.

On July 10, 1975, the Senate Subcommittee on Health of the Committee on Labor and Public Welfare and the Subcommittee on Administrative Practices and Procedures of the Committee on the Judiciary, both chaired by Senator Edward M. Kennedy of Massachusetts, conducted hearings on preclinical and clinical drug related research. In testimony at those hearings, FDA described observations regarding the integrity of animal data submitted in support of the safety of drugs. Problems noted in the investigations of the G. D. Searle Company on Flagyl and Aldactone were presented. From the preliminary investigations, FDA concluded that an indepth study of the experimental animal operations of the firm was necessary and therefore agreed, at the July 10, 1975 hearing, to investigate the animal studies submitted in support of Searle drugs marketed since 1968. These included, in addition to Aldactone and Flagyl, the oral contraceptive Ovulen^{R}, the intrauterine device Cu-7^{R}, and the new animal drug Syncro-Mate^{R}. Subsequently, FDA added the investigational drug Norpace^{R} and the unmarketed food additive Aspartame^{R}.

Scope of Investigation

The Task Force began work in August 1975, by preparing a plan for the investigation which called for:

1. The identification of animal studies conducted by or for Searle and submitted to 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 to conduct the investigation; and

4. Establishing mechanisms for the actual conduct of the investigation at Searle and contractor laboratories.

Several of FDA's Bureaus were requested to review all Searle submissions from January 1, 1968, and to provide the Task Force with a tabulation of the animal submissions according to the identity of the product; the laboratory which conducted the study, (whether at Searle or a contractor facility); the purpose of the study (e.g., reproductive, metabolic, chronic, acute, etc.); animal species; duration of the study; and route of administration of the test substance.

The Task Force established criteria for selecting products and studies for investigation. The essential criterion chosen for selection of products was person-years at risk from exposure to a product with food additives having the highest priority. The selection criteria are described in Attachment 2.

In selecting animal studies for investigation, higher priority was given to the chronic (long-term) studies, because such studies are potential indicators of long-term effects not necessarily monitorable in man. Further, they involve more animals, more observations, more recordkeeping, and more personnel in their performance. The study selection criteria are described in Attachment 3 and the list of studies investigated appears as Attachment 4.

The field aspects of the investigation were conducted by teams composed of qualified drug investigators from various District Offices of FDA and pharmacologists from the Bureau of Drugs and the Bureau of Foods.

The field investigators were selected based upon their proven ability to successfully conduct complex investigations. Mr. Philip Brodsky, one of FDA's most experienced drug investigators, was selected as lead investigator to direct all on-site aspects of the investigation.

anno, Assistant Associate Director for New Drug Evaluation
xicology), and Dr. M. Adrian Gross were assigned full time
ltation to the Task Force and field investigational teams.
rweather of the Division of Biometrics was assigned to re-
tatistical procedures and to provide consultation on statistics

Conduct of the Investigation

Prior to initiation of the on-site phase of the investigation, orientation sessions were conducted for the investigators and pharmacologists. These sessions included descriptions of the problems noted to date, previous experiences at Searle Laboratories during investigational visits by Drs. Kelsey and Gross, and procedures for and legal aspects of the investigation.

Intensive review of all studies selected for on-site investigation was undertaken by FDA pharmacologists assigned to the investigation. Among other things, this review considered the original evaluation of these studies when they were initially submitted to FDA and involved comparisons of the firm's data on individual animal observation records with summaries of such data. During the last week of the "in-house" review, the field investigators joined the pharmacologists to familiarize themselves with the studies and to develop a strategy for conducting the on-site phases of the investigations. The in-house review concluded with an orientation visit to FDA's laboratories to acquaint the teams with some of the practical aspects of laboratory operations.

Initially, the investigation had been planned for 4 teams of two investigators and one pharmacologist each at Searle Laboratories. As a large number of studies were conducted for Searle by Hazleton Laboratories in Vienna, Virginia, the number of teams was expanded to six. Simultaneous investigations were begun on October 6, 1975, at Searle Laboratories and at Hazleton Laboratories.

In July 1975, Searle disclosed for the first time the existence of a pathology report by Dr. Jacqueline Mauro of Microscopy for Biological Research, Ltd. (MBR) of Albany, New York, on rats from the 78 week study on Aldactone received by Searle from Dr. Mauro in March 1973. The report was submitted to FDA by Searle on August 15, 1975, because Dr. James Buzard, Executive Vice President, G. D. Searle Co., was concerned that the report would be uncovered by FDA during the imminent investigation. FDA considered this report to be of such importance that a significant portion of the Task Force investigation of the 78 week study centered around the contents of this report and the circumstances of why it had not been revealed to FDA earlier.

From October 6, 1975 through December 19, 1975, 21 FDA personnel were on-site at Searle Laboratories, Hazleton Laboratories, MBR, or the University of Wisconsin.

There was frequent communication between the Task Force and the investigative teams both by visit and telephone for guidance and direction and determinations regarding the progress of the investigation.

Prior to the arrival of the investigating teams, Searle had assigned over 300 persons from its staff to locate, index, and file the raw data from each of the studies on Aldactone and Flagyl. Additionally, the Searle personnel attempted to do the same for other studies on drugs submitted from 1968 through 1975. Nevertheless a considerable amount of time was expended by FDA just locating many of the records after the teams arrived at Searle. The investigators were informed that Searle had not anticipated

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an investigation of Aspartame and additional delays resulted while the data on the Aspartame studies were located and made available.

On November 24 and 25, 1975, working meetings were held at headquarters between the Task Force and the investigation teams for purpose of:

1. Informing the Task Force and Steering Committee of the findings and status of the investigation of each study to date;

2. Exchanging ideas and information so that one team's investigation could profit from information of another investigation and to determine whether patterns of problems with the studies had begun to surface;

3. Assisting the Task Force in determining whether the investigation should continue, and if so in what area and for what period of time, or whether termination should be recommended for any part of or all of the investigation.

The majority of the field investigative work was completed by December 19, 1975, but only a few of the investigation reports had been completed. All of the reports were completed by mid February, 1976.

Analysis of a number of the reports revealed the need for selected follow-up investigations or visits to Hazleton, Searle, University of Wisconsin, and MBR, to obtain further facts regarding a number of the preliminary findings.

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From January through March 1976, the reports of the individual study investigations were reviewed to determine patterns of practices and their significance.

Findings of the Investigation

In the testimony presented by the Commissioner on January 20, 1976, preliminary findings were presented on a product by product basis. While the Task Force continues to support those findings, it has elected to submit this report on the laboratory practices of Searle for the conduct of animal research. The Steering Committee is referred to the inspection reports for specific findings on individual products.

The full findings of this investigation are included in each of the reports covering 25 individual studies. These reports, in excess of 500 pages and their exhibits, in excess of 15,000 pages, are available for reference. The findings here, therefore, represent only a distillation of the findings contained in the individual reports. The Task Force has selected only those findings for inclusion which it feels to be among the most significant or most representative of the findings noted throughout the individual study investigations. The investigators' reports are only representative of errors and discrepancies noted. No attempt was made to quantify all the problems associated with a particular study.

Chemistry or Pilot Plant Operations

Review of the manufacture or synthesis of the test substance included specifications of the product, and analysis of the product for purity and stability prior to use. A review of the inspection reports disclosed a number of discrepancies in these factors. Included were the failure to

ow-up for confirmation and/or correction an analysis which disclosed a uct to be out of specification, and a failure to maintain adequate re- s of batch preparation, assay, and release of products used.

the Ovulen 7 year dog study the investigators reported that Searle's alytical laboratory reported test values on Ovulen tablets in 1972, 1973 d 1974 that were higher than the original analytical values in 1968. It is found that some of the lots were super potent using the firm's own pecifications for the commercial Ovulen product. Searle took no action o resolve these discrepancies until they were pointed out by the FDA investigators.

In the Aspartame (DKP) 115 week rat study, the submission states that twelve lots of the test compound, diketopiperazine, a metabolite of Aspartame were manufactured by a Searle chemist and used in the study. However, the investigators found that some of the batch numbers were merely different drum numbers and actually only seven batches were made. Searle personnel informed the investigators that records of manufacture and assay of two batches could not be located.

In the Norpace 52 week dog study, three lots of the product were manufactured in a pilot plant by a Searle chemist. Batch records for these lots were the chemist's laboratory notebook pages only. There were no written specifications available for that time period, but a 1970 specification stated 202-210°C for the melting range and a 1965 physical description stated 200-208°C with decomposition. The melting points for the three lots used were, respectively,

209-211°C, 204-206°C, and 198-200°C with decomposition. Thus, doubts are raised about the identity and purity of these lots. Further, there were no records to indicate release or approval of the drug substance used.

While the Task Force itself is unable to determine whether the problems noted in the manufacture and analysis of the test substances were significant factor which could have compromised the studies, the chemistry and manufacturing aspects of product used in animal studies must be included in good laboratory practice regulations.

Protocol

At Searle, protocols were generally prepared within the Path-Tox Department with consultation in some instances from the Mathematics and Statistics (Math-Stat) Department. They were generally reviewed and approved by the director of the Path-Tox Department and submitted for evaluation and approval to a Protocol Design Committee composed of (1) a biostatistician, (2) a biology research assistant director, (3) a research committee representative, (4) a clinical representative, (5) the pathology-toxicology department monitor, and (6) the PT department advisor for the product. Not all of the six competencies noted were always included on the review of any particular protocol.

Significant deviations from the protocols of several studies were noted which may have compromised the value of these studies, including the

of tissue masses from live animals during the course of a study.
s no indication that these deviations were reviewed or approved by
tocol Design Committee; hence they may represent serious unauthorized
s in the experiments. In the 78 week Aldactone study written changes
ıade on three occasions. These changes were approved by Dr. R. G. Mc-
ll, Director, Path-Tox Department, without prior concurrence by the
ɔcol Design Committee; on at least one occasion the protocol was amended
ly by Dr. McConnell without a written document to follow. In at least
study, the Aspartame 52 week monkey study, the protocol was written
er the study had been initiated.

ıe investigators sought to determine if written protocols were available
or each study. Protocols were produced for all studies investigated with
the exception of the five Flagyl reproduction studies, where a protocol
was available for only one.

Thus, while Searle had an available mechanism to evaluate and approve proto-
cols prior to the initiation of research and during the course of the
experiment, this mechanism was not always used. In some instances, experi-
ments were started without prior review and approval by this committee and
the investigators could find no evidence that the committee was used for
amendments to existing protocols while studies were in progress. There is
evidence that not all changes in protocols were promptly committed to writing
prior to the time the changes were actually implemented.

Chronology of Studies

Each of the studies was reviewed to determine Searle's practice and performance in adhering to established schedules for animal research and to determine whether or not inordinate delays occurred in the conduct or completion of studies and their reporting to FDA.

Monthly records prepared by Searle's Path-Tox Department, found by the investigators (Attachment 5), outline the status and anticipated dates for completion of projects underway at Searle Laboratories. The cover memorandum of December 18, 1975, by Dr. McConnell describes their use in his department. A random review of these sheets disclosed a segment II reproduction study in rabbits initiated in July 1968, where the animals were necropsied in December 1968, was actually not submitted to FDA until June 1974. Thus, a study which could have been completed and reported to FDA in less than one year took six years to complete and submit.

The Aldactone 78 week rat study (underlined in Attachment 5) was initiated in August 1970. The design called for the study to run 78 weeks and the antemortem phases to be concluded in February 1972. Animals were necropsied in February and March 1972. The slides were not sent to the contract pathologist (MBR, Ltd.) to be read, until November and December 1972, a period of some eight to nine months after the time the animals were necropsied. MBR reported its findings to Searle in March 1973; its report was acknowledged by a letter from Dr. McConnell on June 1, 1973, which stated "The

t has now been reviewed, it looks just fine...." In August 1974, some
onths after the MBR report had been submitted to Searle, the slides
sent to a second pathologist, Dr. Donald A. Willigan (DAW, Inc. of
nd Brook, New Jersey). Dr. Willigan's report was received by Searle in
ember 1974. FDA was advised of Dr. Willigan's findings in January 1975,
a report was submitted in March 1975. This report included only the
thology report by Dr. Willigan and failed to include the report of MBR.
t was not until August 1975, after the FDA investigation had been initiated
hat Searle submitted the report of MBR to FDA. (A comprehensive chronology
appears on pages 6 through 9 of the investigation report of this study).

There are two factors of serious concern regarding the delays encountered in the submission of the Aldactone 78 week rat study. The first is that a study initiated in 1970, with animals necropsied in February and March 1972, should have been reported to FDA before 1975. The second is that when Searle received the report of MBR in March 1973, it did not report these findings promptly to FDA. The histopathological evaluation by Dr. Jacqueline Mauro (of MBR) constitutes, in FDA's opinion, alarming findings as Dr. Mauro's report shows a dose related increase in benign tumors of the liver and testes which should have been reported promptly pursuant to section 505 of the Federal Food, Drug, and Cosmetic Act and the Agency's implementing regulations.

The 104 week Aldactone study conducted for Searle by Hazleton Laboratories was initiated in September 1970. Hazleton submitted a draft report to Searle in May 1973. Searle did not return this draft, annotated with corrections,

until August 1974, some 16 Months later. Hazleton completed its report and submitted the final version to Searle in November 1974, and Searle transmitted its report to FDA in January 1975. Here again, a study which could have been completed and reported to FDA in early to mid 1973 did not reach FDA until 1 1/2 years later.

Except in the case of the 52 week monkey study of Aspartame, the Task Force has been unable to document whether or not management above the Path-Tox Department was aware of the status of studies underway in Searle's own laboratories, or for Searle under contract.

For example, in a meeting of FDA's investigators with Dr. Robert A. Moe, Senior Vice President, Scientific Affairs and Dr. Paul D. Klimstra, Vice President of Preclinical Research and Development, on December 17, 1975, Drs. Moe and Klimstra claimed they did not receive the monthly scheduling and planning documents, i.e., Attachment 5. Further, in a November 6, 1975 interview, Dr. Moe indicated he did not learn of the MBR pathology report of the Aldactone 78 week rat study until after the June 10, 1975 meeting of Cardio-Renal Drugs Advisory Committee.

However, Searle representatives, in a recent meeting at FDA, expressed particular concern about statements in the January testimony that portended changes in the labeling for Flagyl and Aldactone. They pointed out that Aldactone and Aldactazide (a combination with hydrochlorthiazide) are Searle's largest selling products (34% of pharmaceutical sales, $87 million,

in 1974). They indicated quite clearly that the firm would resist any effort by FDA to impose label restrictions that would curtail use of the drug, spironolactone. They described the financial consequences of curtailed use as "drastic," and referred to the stakes as "very high."

In addition, we found evidence that, as far back as 1969, top management concerned itself with the animal studies to determine the safety of its artificial sweetener, Aspartame. Management knew full well the economic potential of Aspartame. An internal strategy memorandum from the Regulatory Affairs Department to top management advises management of tactics designed to produce favorable action by FDA officials and concludes that Searle must get Aspartame into commercial channels as soon as possible to minimize the incentives of other firms to develop other sweeteners. The author of the memo anticipates the economic potential of the product, given FDA approval, when he states, "Actions in the U.S. will tend to influence the actions in other countries as well." Therefore, the Task Force views with some skepticism the claims of unawareness by Searle management of the status of studies affecting these important products.

Personnel and Supervision

Important on the operational level in terms of responsibility for safety studies on a product at Searle, are the P-T (Path-Tox) Advisor and P-T Monitor. The P-T Monitor is responsible for outlining a program for pre-clinical safety evaluation of products to which he is assigned, including designing protocols, monitoring the progress of each study, assuring the appropriateness and adequacy

of the data as well as interpreting the data from each study and preparing the final draft report of the study.

The P-T Advisor acts as a consultant to the P-T Monitor and has senior responsibility for the appropriateness, adequacy and interpretation of data from the studies. He is also responsible for the final departmental sign-off on any report generated by the Path-Tox Department.

Obviously, the length and complexity of the types of studies performed by the Path-Tox Department, even assuming the best recordkeeping, makes crucial the full attention and continuity of key personnel.

The lack of continuity of supervision can be seen in the 78 week Aldactone study, which from its inception until reporting to FDA, had four different monitors during five different intervals and three different advisors. Further, records indicate that for a period of 11 months there was no monitor or advisor at all for this study.

As will be discussed under Observation of Animals in this report, there was little continuity of technicians that performed antemortem observations on animals from one observation period to another. In addition to a lack of continuity, there was a lack of adequate supervision and training of the technicians in all phases of the studies, which is documented in the Cu-7, Norpace dog, Norpace rat, Aspartame (DKP) 115 week rat, and Aspartame 42 week hamster investigation reports (the details of some are discussed later).

Dr. McConnell functioned simultaneously as P-T Advisor and P-T Monitor in some studies, a practice which would seem to rule-out any possible check and balance inherent in a separate advisor/monitor system. Of those studies investigated which were conducted at Searle, Dr. McConnell was P-T Advisor on at least 9 and P-T Monitor on at least 11. Further, he served as consulting pathologist and as supervisor of the prosectors in rat necropsies on at least five other studies, and was supervisor of all the Flagyl reproduction and teratology studies. In addition, he was responsible for the administration of the Pathology-Toxicology Department.

Antemortem Phases

In each study investigated, poor practices, inaccuracies, and discrepancies were noted in the antemortem phases which could compromise the study.

Selection of Animals

Protocols normally specified age and sex requirements of animals. In general, these criteria were followed. However, exceptions were found in the 106 week dog study of Aspartame, where the protocol called for dogs to be 150 to 160 days of age and yet three dogs were used in this study that were approximately 70 days older than the protocol specified. In the Norpace 52 week dog study the protocol specified that animals were to be 9 through 15 months of age; however, the dogs placed on this study ranged from age 5 to 53 months.

Quarantine Practices

Dr. Theodore W. Harris, Manager of Veterinary Services, stated that at Searle there are no established procedures for quarantine or acclimatization for rodents.

At Hazleton Laboratories rats and mice were said to be held for a two week period before they are entered into a study. In the 104 week rat studies of Aldactone and of Aspartame there were deviations from this holding period when rats were introduced into the studies after only five or six days respectively.

Identification and Randomization of Animals

Rats, hamsters, and rabbits are not individually identified; only the cages are identified with color coded tags. Dogs are identified by being tatooed on the ear by their supplier prior to their shipment to Searle. The supplier's number is used for identification until the dog is assigned to a study. A similar system is employed by Hazleton Laboratories.

Computer generated random numbers are used for assigning the dose and housing groups. Cages of control and treated rats were arranged on the same rack as shown by the diagram in Exhibit R-15 of the inspection report of the Aspartame 115 week rat study (Attachment 6).

1975

Individual feed jars were not identified either by color code or rat number. At feeding intervals, the feed jars were removed from the animal cages and placed in rows on a cart according to the diet, (e.g., control, low level, middle level, high level); and their positions on the rack is shown in Exhibit R-17 of the same report (Attachment 7).

When the jars are placed on the cart in the manner employed by Searle, the process of weighing feeder jars and replenishing the feed requires the utmost care to assure that the proper feed mixture is placed in the jars and the jars are correctly returned to the rack. The amount of care required to prevent an error is time consuming.

Observations and weighings were normally conducted weekly for the first four weeks of the study, once every two weeks for the next eight weeks, and every four weeks thereafter for the duration of the study. In our review of some of the records of the Aldactone 78 week rat study, we noted that food was replenished weekly. The random arrangement of the animals on the rack necessitates operations in food replenishment which can enhance the chance of errors.

The probability of mix-up is further illustrated when the following is considered: Assuming that a rack of 24 cages could be processed in a period of one hour, an experiment requiring 360 rats would take 15 hours for weighing, examination, and feed replenishment. Therefore, it would take one technician two days out of a week to complete the weighing and feeding operations for one experiment. Considering the number of experiments being conducted simultaneously, (during the period of February, 1969 to May, 1970, there were 12 rodent studies, 11 dog

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studies and other animal, e.g., rabbit and pigeon, studies being carried out) feed replenishment and the other experimental procedures of a sophisticated toxicology study would have consumed considerable time to prevent error. Considering the number of technicians employed at one time during this period and the amount of time required to carry out all of the necessary procedures including necropsies, it is inconceivable that these operations could have been carried out without error. Evidence of this conclusion is seen in the manner in which the "Observation for Drug Effect" sheets were completed.

During an interview with Mr. Tony Martinez on December 17, 1975, the investigators asked him to estimate the time necessary to weigh and observe a rat and to obtain the initial and final feeder weights. Mr. Martinez stated that early in a study about three minutes per rat would be adequate but as the study progressed and lesions appeared in the rats, it would probably take longer. In the investigation of the Flagyl 80 week study the investigators noted that about 45-50 minutes were required to weigh, feed, and examine a group of 24 rats early in the study. Toward the end of the study this same process took about 20 minutes. While it is noted that the total number of animals decreased only very slightly through some deaths, it also appears that the amount of time spent in examinations and weighing and replenishment of food decreased disproportionately.

Treatment Mixtures

One of the most elementary considerations in a toxicological study is to assure that the test animals receive the active ingredient under test.

When the substance to be tested is incorporated into the feed, its homogeneity and concentration in the diet mix should be determined prior to the start of the study. Random samples from freshly mixed batches should be analyzed periodically during the course of the study to ensure that the proper mixing and formulation procedures are being used. In studies conducted by both Searle and Hazleton, little concern was evidenced for the need of proper quality control of homogeneity, concentration, or stability of the active ingredient-diet mixture.

When Dr. Frederick Reno of Hazleton Labs was asked why Hazleton did not conduct tests on the purity of the test substance, he replied that Hazleton's policy is that the purity of the test material is assumed to be 100% unless notified to the contrary by the client. Tests for stability, potency, and homogeneity of the treatment feed mixtures are performed only at the client's specific request; Searle never made such a request of Hazleton in its protocols. Further, Dr. Reno stated that Searle never requested that the basal feed be assayed for residual drugs, pesticides, or any other contaminants. Hazleton did not conduct such tests for Searle nor were any reserve samples of the treatment mixtures maintained for studies performed for Searle.

It was noted in the investigation of the Aspartame (DKP) 115 week rat study that drums of the product for each of the dosage levels were identified with color coded labels to match the color of the identification card on the animal cages. When the animal rooms at Searle were inspected on October 17, 1975, it was noted that each drum contained

several labels pasted over one another and that the labels underneath the current labels were of various colors. If the current label were to come off the technician could easily be misled by the label underneath resulting in a feed mix-up. This is the only study where we found evidence of a test for stability of the test substance in the diet mixture, but the value of this test was negated when, during the course of the study, there was a change in the supplier of the diet and new stability tests were not performed on the new diet-test substance mixture.

In preparing mixtures of active substance with food both Hazleton and Searle used blenders that were not electrically grounded. This is of concern because of the potential for the electrostatic properties of the test substance to cause it to adhere to the metal walls of the mixer and/or to distribute unevenly through the food, thereby preventing a nomogeneous food-test substance mixture.

In view of the problems noted with all stages from the receipt of the test substance, preparation of the feed-test substance mixture, the failure of both Searle and Hazleton to analyze for concentration, homogeneity, and stability of the test substance in the diets; and the practices of feed replenishment, there is no way in which it can be assured that animals received the intended dosages.

1979

Animal Facilities

In reviewing Searle's facilities it is not possible to comment on the condition and practices employed in those facilities at the time the studies were conducted. However, investigators toured the animal facilities on October 17, 1975, and noted the following poor current practices at that time:

> An exterminator company is employed by Searle for general pest control in the animal rooms. This company has a blanket order to spray the animal rooms twice a month and additional instructions may be given for specific animal rooms as required. Pyrethrum (piperonyl butoxide) is sprayed by means of a fogging machine for two or three minutes. The legs and wheels in the animal racks are painted with another insecticide.
>
> The investigators were informed that animals are not removed from the animal rooms during the time that they are being fogged with insecticides. Evidence indicates that this practice has been in effect at least since 1970. A memorandum dated September 25, 1970, from Dr. McConnell to Dr. Victor Drill, which appears as a General Exhibit to the Aspartame inspection report, indicates that Dr. McConnell was concerned about this practice at the time, however, there was no evidence that this practice was ever discontinued.

The investigators inquired whether basal diets or treatment mixtures were subjected to analysis for pesticides. No records were found to indicate that any treatment mixtures used in the studies were ever tested or assayed for pesticide content.

Currently a mixer with a capacity of 10 to 12 kg. is used for blending treatment mixtures. The investigators were informed that the mixer is cleaned with water, alcohol, ether, or is dry cleaned, depending on the material blended. When the mixer was examined on October 17, 1975, however, it was encrusted with material from previous use.

Records are not maintained of weighing and blending of treatment mixtures. After mixing, the mixtures are placed in plastic, teflon lined containers and are identified with color coded stickers. The colors corresponded to the identification tags on the animal cages. When the investigators examined the containers on October 17, 1975, they noted that the identification stickers of different colors were present underneath the current stickers and that the edges of some of the top stickers were raised.

Running inventory records for either treatment mixtures or the test compound used in treatment mixtures are not maintained. Dr. K. S. Rao, Senior Research Investigator (Toxicology), indicated that he felt that it is not necessary to maintain such records as fresh treatment mixtures are prepared weekly, bi-weekly, or every four weeks. Clearly, the lack of inventory records, the lack of batch records, and the lack of homogeneity or stability assays, results in poor control over the treatment mixtures.

The practices enumerated above are such that any or all of them could compromise the integrity of a study.

Observation of Animals

As stated previously, rats were observed for pharmacological activity of the test substance and for tissue masses at one week intervals during the first four weeks, once every two weeks for the next eight weeks, and monthly thereafter. The investigators were informed by Dr. Rao and Mr. Martinez that technicians of the Path-Tox Department observed animals for survival once each day on weekends and once or twice per day on normal work days. When an animal was found dead, the identification was removed from the front of the cage and the animal was either necropsied promptly or fixed in preservative in-toto.

Technicians participated in many studies simultaneously. The technicians weighing, withdrawing blood, feeding, and observing the animals for tissue masses, etc., were not assigned to a particular study, but performed those functions for various studies in progress. Usually, teams of two technicians were responsible for the antemortem observations and their documentation. The normal procedure employed by the Path-Tox Department was that daily observations were made in pocket notebooks or on scraps of paper and these observations were later transferred to data sheets called "Observation for Drug Effects" sheets (Attachment 8) on which each animal was listed numerically and the presence or absence of certain physical and behavioral characteristics and lesions were noted. There is a space at the heading of these sheets for the name or names of technicians; these forms sometimes did not contain any names.

Technician Bartolome Tangonen stated that the appearance of his initials at the top of a page did not necessarily mean that he actually made the observations described in the sheets or that he filled out the sheets which bear his initials. His initials could indicate that he was supervising the work of other technicians or that he was making the observations.

Numerous errors and inconsistencies were noted in all of the antemortem phases of these experiments. For the 78 week Aldactone rat study, a table constructed by the Task Force (Attachment 9) identifies the

technicians whose names appear on the Observation for Drug Effect sheets for the 12 animal groups during the 25 observation periods required for this experiment throughout the 78 weeks. Because many of the observations required are of a subjective nature, continuity of the persons assigned to make these observations is critical, yet the names of the observers entered on the same animal groups are often different for subsequent observations. Further, names appeared on these sheets for only the first half of the experiment; no names appear on these sheets from the 40th week through the 78th week, making it impossible to determine who made these observations.

Inconsistencies were noted in observations of findings during the course of the Aldactone 78 week study with animals being reported as alive when they were actually dead, and in the reporting of the presence and location of certain tissue masses. These included approximately 20 irstances of animals reported as dead and then reported as having vital signs normal again at subsequent observation periods. (See Attachment 10)

Similar inconsistencies are contained in the Flagyl 80 week rat study, the Cu-7 rat study, the Aspartame (DKP) 115 week rat study, and in the Aspartame 46 week hamster study.

With regard to discrepancies in the observation and recording of tissue masses and other conditions the following are representative examples:

In the Aldactone 78 week rat study, a mass was observed in

animal G8MM on the 36th week, allegedly by technician David Kie. The mass was not reported on the observation record for the 40th week but it was reported again on the 44th week and not reported again on the 48th week. The observation records did not bear the name of any technician for the 40th, 44th, or 48th weeks. In the 52nd week the sheet (technician unidentified) bore the notation that the animal was dead. In the 64th week of the study the animal was reported as being alive but there was no mention of a tissue mass and the observation sheet did not contain the technician's name.

In the 40th week a tissue mass was observed in animal M21CF; neither initials nor name of the technician was present on the form. In the 44th week the mass was not present for that animal but a notation of "mass larger" was listed for animal M22LF, which appeared in the line below M21CF and for which no mass had been reported earlier. In the 48th week of the study the mass from animal M22LF was no longer reported, however, there was a notation that the mass of animal of M21CF was larger. Throughout the remainder of the study from the 48th through the 78th weeks the tissue mass of animal M21CF was consistently noted as being larger (or "bigger"). At necropsy this mass was found to be 12cm x 9cm x 4cm in the thoracic-cervical region.

Additional examples from this same study of the manner in which observations of tissue masses are recorded include the following:

1. Animal J16 is described on 2/23/72 under "Tissue Masses - Lesions" as having an abscess in the left inguinal region which is "larger"; no mention of any such abscess is reported for any prior observation.

2. On 12/14/71 animal B26 is listed under "Tissue Masses - Lesions" with its mass as larger, but no tissue mass in this animal was previously reported. Four weeks later, on 1/12/72, a tissue mass is reported to have been initially detected.

3. Animal B27 is reported on 9/21/71, to have developed a tissue mass. At the next observation period, 10/19/71, the mass is reported as unchanged; on 11/16/71 the mass is indicated to have regressed; on 12/14/71 and 1/12/72 this animal is reported to be free of tissue masses; on 2/8/72, the next observation period, the mass for this animal is stated to be the same.

4. Both animals A2 and A3 are described on 9/20/71 as having developed tissue masses. At the next observation period, 10/8/71, both of these animals are reported as being free of any tissue masses, while at the observation

period of 11/5/71, the records indicate that both of these masses regressed.

5. Animal E3 is described on 7/1/71 as having a tissue mass initially reported on that day; the following are the reported results of the six subsequent examinations:

7/29/71 - check, indicating normal
8/26/71 - "mass same"
9/23/71 - "mass same"
10/21/71 - check, indicating normal
11/08/71 - "mass same"
12/06/71 - "mass regressed"

6. On 9/23/71 Animal E9 is stated to have developed a tissue mass. The following are the results of the four subsequent examinations:

10/21/71 - "mass regressed"
11/18/71 - check, indicating normal
12/16/71 - "mass regressed"
1/13/72 - check, indicating normal

7. Animal D29 is reported as having a tissue mass on

7/1/71. The following are the reports of the seven subsequent examinations:

7/29/71 - check, indicating normal
8/26/71 - check, indicating normal
9/23/71 - "mass same"
10/21/71 - check, indicating normal
11/18/71 - "mass regressed"
12/16/71 - "mass same"
1/13/72 - check, indicating normal

8. Animals H26, D12, K25, D5, K17, and D19 each are reported to have developed more than one tissue mass; in each case, however, observations made subsequently fail to distinguish to which tissue mass they apply.

In the Supplementary Statement of Mr. Daniel C. Searle dated February 13, 1976, which was appended to the record of the Joint Hearing before Senator Kennedy held on January 20, 1976, Mr. Searle, referring to the errors on Observations for Drug Effects sheets, stated "In the truest sense, the errors identified by the FDA (in these records) were completely irrelevant to the scientific conclusions of the study..."

His comment on the irrelevancy of the mistakes on these records relates to his testimony that other records with information as to date of death

and tissue masses were kept by Searle and that these other records contained the "correct" information.

We do not agree with Mr. Searle that the information on the Observations for Drug Effects sheets is irrelevant.

The title printed on these "Observations for Drug Effects" forms is "Statistical Work Sheet"; it is therefore reasonable to expect that these "careless" entries must have formed the basis for input for statistical operations which are crucial to the "scientific conclusions of the study." The methodology used in these statistical operations at Searle (the Horton and the Sachs Life-Table procedures) depend completely on the time a certain tissue mass (tumor) is observed and on the time the animal with the mass (and all other animals in that group) died. If the alive/dead status of each animal was "carelessly" entered on these "Statistical Work Sheets", as conceded by Mr. Searle, and if its status as a tumor-bearer at any time was largely in doubt, as demonstrated here, the statistical computations based on this kind of raw input data are of questionable value, if any, and would clearly affect what Mr. Searle denominates as the "scientific conclusions of the study".

Errors in observations are not limited to tissue masses. In the Flagyl 80 Week Study the investigators noted that an observation of a cloudy left eye in animal A23 early in the study was reported on sub-

sequent dates to move the animal's left eye to its right eye, from animal A23 to animal B4, to animal C23, then E23, and finally to animal D23. Interspersed with these movements between different eyes and between different animals were weekly observations which either made no mention of a cloudy eye at all or made comment on the change in the severity of the condition. From the first observation on December 27, 1966, to the last observation on October 31, 1967, there is no continuity of observations to assure which animal had the cloudy eye and which eye was, in fact, cloudy. Only at necropsy was the confusion ended when only animal A-23 was found to have a cloudy right eye.

A cloudy eye is easily detectable. That this condition appears to come and go, move from one eye to another, and from one animal to another speaks eloquently of the unreliability of Searle's antemortem observations and records.

Absorption Determinations

An important consideration in toxicity studies is the determination of absorption of the test substance. The eliciting of a pharmacologic effect or the measurement of a systemic response have been relied upon in the past. With the development of more sopnisticated methodology and the evolving discipline of drug metabolism, the measurement of blood or

tissue levels of a chemical or its metabolites affords a more precise determination of the absorbed test substance.

In the Norpace 52 week dog study there was evidence to indicate the drug substance was being absorbed. Plasma drug concentrations were measured periodically for the first 26 weeks and appeared to show dose response relationships. However, in Searle's submission to FDA, the blood level reported for the 40th week for the high and mid-level dosage groups, which upon our investigation was found to actually have been a 49th week sample of blood, was considerably lower than had been anticipated and lower than the reported levels on previous and subsequent weeks. Searle's explanation to the investigators for this unexpected result was that it was probably due to a methodology problem. However, apparently no steps were taken to determine the cause of this drop in blood levels. There is the possibility that the animals were not dosed at all or that the time between dosage and blood sampling differed appreciably on this occasion. However, no records were kept of the number of capsules prepared for each animal, or for drug administration, and records of time of administration and time of withdrawal of blood were also not available.

Searle also considered bioavailability in their Flagyl reproduction studies. The problems encountered will be discussed later in this report. (See page 63)

Excision of Tissue Masses From Live Animals

In the Aldactone 78 week rat study, the 115 week rat study of Aspartame, and in the Ovulen 7 year dog study, tissue masses were excised from live animals during the course of the study and the animals were continued on the study.

In the Aldactone study one mass was removed from each of three animals. The explanation for this practice offered by Searle was that these masses were in the head and neck area and prevented the animals from obtaining food. It was stated that unless these masses had been removed the animals would have starved to death. However, all the tissue masses were in the axillary area and were reported as 1 cm in size. Also, apparently no consideration was given to enlarging the orifice in the feeder jar to permit the animal access to the food without removing the growth. Recall also the 12X9X4 cm mass in the cervical thoracic area of M21CF which was not excised (see page 44 of this report).

In the Ovulen 7 year dog study a fibroadenoma of the abdomen was removed from one animal and the animal allowed to continue on the study. In the Aspartame 115 week rat study on February 10, 1972, a tissue mass was excised from one animal; in two other instances incisions were made in the skin over tissue masses, however the masses were not removed. The explanation offered for this latter practice was that the persons responsible for the conduct of the study wanted..."to see what was inside."

It is interesting to observe that an unsigned note of a meeting of May 27, 1971, attributed by Dr. McConnell to Mr. Martinez, stated that if additional masses appeared in animals in the Aldactone 78 week rat study, they were not be be excised. However, in the Aspartame 115 week rat study, the practice recurred.

The removal of tissue masses from rats in a chronic toxicity study is an unacceptable practice, since it may seriously prejudice the findings of the experiment. For example, if the removed mass, when excised, is found to be benign, as happened with animal H27LF in the Aldactone 78 week study, its excision may have prevented it from becoming malignant, a change which is not unusual, and which is normally a function of time. The purpose of a safety study in animals is to find out as completely as possible all the likely risks associated with the test products. Interference with the natural development of tumors will prejudice the findings of the experiment.

Postmortem Phases

Procedures for Animals Found Dead

Animals found dead during the course of a study should be necropsied promptly; when prompt necropsy is not possible, the animal remains should be refrigerated until the next working day, when the postmortem examination must be performed. Delay or improper handling of dead animals results in the loss of valuable information through autolysis

of tissues. Proper practice following necropsy is to fix the tissue in freshly prepared neutral buffered formalin after slicing the organs and opening the respiratory and digestive tracts to permit penetration of the fixative to prevent autolysis.

In a number of the studies which we investigated at both Searle and Hazleton, loss of information through autolysis of tissues was substantial. While Searle's submissions to FDA stated that animals were necropsied promptly after death, FDA investigators found that this was not always true; frequently animals were fixed in-toto after opening only the thoracic and abdominal cavities and holding them for periods some times longer than a year before they were necropsied. Fixation in-toto is an unacceptable practice and its use by Searle had to contribute to tissue loss. At Hazleton, there was no evidence of fixation in-toto. However the unacceptably high incidence of autolysis, 14%, in one study, indicates improper handling of the tissues.

In the Aspartame (DKP) 115 week rat study at Searle 98 of the 196 (50%) animals that died during the study were fixed in-toto for periods ranging from 1 day to 1 year before they were necropsied. Of these, 20 animals had to be excluded from postmortem examinations because of excessive autolysis. Dr. K. S. Rao realized that Searle's procedures with regard to delays in necropsies were not proper. In a memorandum to Dr. McConnell dated July 13, 1973, Rao stated, "I realize animals which die during the

study are the most critical ones to evaluate the compound effects. Hence, our people are now ready to perform a complete autopsy of the dead animals. If there are any special instructions in handling the brain and spinal cord, please advise.", (Exhibit R-64 to the Aspartame 115 week rat study). However, Dr. Rao did not write this memorandum until 78 weeks into this study. Of the 20 animals in this study which had to be discarded because of excessive autolysis, 13 died prior to Dr. Rao's memorandum; the remaining 7 died subsequent to that memorandum, indicating that his recommendation for prompt necropsy was not followed. In fact, Searle's records show that only 3 of the 20 animals were necropsied on the day they were found dead. Similarly, in the Aldactone 78 week rat and the Aspartame 46 week hamster studies, a number of animals that died were fixed in-toto and necropsied at a later date.

Necropsy Procedures

Professional personnel performed dog necropsies, while the necropsies of rodents were generally assigned to technicians who were supposed to work under the general guidance of a professional. Necropsies of dogs were done by professionals, Eugene Youkilis, Ph.D. (pharmacologist), Roger Hemm, Ph.D., (experimental pathologist), John W. Sagartz, D.V.M. (Veterinarian) and Joseph H. Smith, M.D. (pathologist). Dr. Robert McConnell did some of the necropsies of rats and dogs. Necropsies of rodents were performed primarily by technicians, Tony Martinez, David Kie, and Robert Spaet.

Searle had no formal training program for its prosectors; its on-the-job training was minimal. An example of this is shown in the Aspartame (DKP) 115 week rat study where the necropsy of the animals was performed by Mr. Spaet. His written observations of gross pathology were later changed by Dr. Rudolph Stejskal, who was the supervising pathologist on this study but who was not physically present during these autopsies. When questioned by the investigators as to why he made these changes, Dr. Stejskal stated that Mr. Spaet was employed for only a few months and was encouraged to write down everything that appeared to be questionable or unusual. He also informed the investigators that Mr. Spaet sometimes used wrong terms in the description of his findings. The gross pathology observations submitted in the Food Additive Petition were selected by Dr. Stejskal and represented his interpretation of Spaet's observations. Dr. Stejskal indicated if he could not confirm a gross observation microscopically, he would then omit tne gross observation from his report. As a result, Dr. Stejskal omitted many gross observations which could not possibly be confirmed microscopically. Had a professional been available to confirm Spaet's findings directly or to provide him with a practical on-the-job training during necropsies, then it would not have been necessary for Dr. Stejskal to haveto change or "second guess" Spaet's observations. Morever, Mr. David Kie, a more experienced prosector, was also available during these necropsies and did some of the prosecting himself. Review of the gross pathology records disclosed that, in at least one instance, Dr. Stejskal omitted a statement made on the gross observation sheet by Mr. Kie.

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In the Norpace 40 week rat study the necropsies were done by technicians Martinez and Kie. Dr. McConnell, who was supposed to be supervising pathologist for this study, was not present during any of these necropsies. During an interview with Dr. McConnell the investigators asked if he remembered being called for consultation by the prosectors. Dr. McConnell relied, "I don't recall, and I'm not surprised that I don't recall. This compound was a...I don't recall any compound related effects nor compound unrelated effects." Dr. McConnell stated that this was a "very clean study." He informed the investigators that the pathologist was called only if "an experience prosector" had a question. Other examples of inadequate supervision of necropsies were noted in the Flagyl 80 week and the Cu-7 studies.

The records of postmortem examination are similar to those of antemortem observation in that they are often unsigned and undated; the firm could often not explain the significance of a person's name or initials even if they appeared on the form. In the Cu-7 study, the investigators found a memorandum by Dr. McConnell to the prosectors dated October 14, 1971, directing them to sign the autopsy records. Despite this directive, neither Dr. McConnell nor Mr. Martinez could identify who had performed necropsies on specific rats in this study (in addition to normal necropsy procedures this study required the microscopic dissection of the uterine horn of the rats). Further, the investigators observed crossed out observations on one necropsy sheet which had not been initialed nor dated by the person who deleted the comment; there were instances where comments

made on these records did not bear initials or dates and were written in a different style handwriting but were stamped with the name of Tony Martinez. According to Mr. Martinez, the presence of this stamped name did not necessarily mean that he had actually done the necropsy or had directly supervised it. Mr. Martinez was questioned regarding his supervision of Mr. Kie during prosection. He indicated that Mr. Kie would consult him only if unusual abnormal findings were encountered and that if Kie did not note anything unusual in an autopsy he, Martinez, probably never looked at the rats that Kie examined.

Histopathology

Histopathology is an extremely important morphological indicator of the effects of an insult upon a tissue or cell. Careful preparation, cutting, slicing, mounting, staining, and interpretation of histologic slides from animal tissues to determine the changes occurring in test animals during the course of, and to some extent, as a result of the administration of a test substance to the animals, is crucial if the investigator is to glean valuable information from the experiment. Much valuable histopathologic information was lost in some of the studies which we investigated at Searle and Hazleton through preparation of poor quality slides which could not be interpreted by pathologists; inadequate numbers of acceptable quality slides of certain tissues upon which conclusions were based; and violations of protocol specifications which called for slides

to be made of certain tissues for histopathological evaluation which was not done.

In the Aspartame (DKP) 115 week rat study at Searle the protocol called for one-half of each kidney to be serially blocked and frozen and four blocks of liver to be frozen. There were no records to confirm that this was done; the investigators were informed that frozen sections were not taken of liver or kidney. Further, the protocol specified that female mammary tissue only was to be imbedded, however, the investigators were informed that mammary tissue was examined from both male and female rats. The gross pathology report for animal J1CM had a notation by the histology technician that mammary tissue was not included among tissues submitted for sectioning. The submission to FDA is misleading because it implies that mammary tissue from this animal was examined and found unremarkable when, in fact, no slides had been prepared of mammary tissues for this animal.

In the Aspartame 104 week rat study at Hazleton 3 tissues were noted on single animal autopsy sheets as having usual or unusual lesions and yet, contrary to the protocol, slides were not prepared of this tissue for microscopic examinations. In the Ovulen 7 year dog study, 5 out of 8 animals had fewer tissues examined microscopically than were scheduled in the protocol.

In the 52 week dog study of Norpace, FDA requested readings of the slides

in the high dose animals. Slides prepared at Searle were sent to Hazleton for reading. Dr. Robert B. Kwapien of Hazleton reported that of the 16 slides submitted, 13 had artifacts which precluded their evaluation. The tissue blocks were available and yet new slides were not made so that an accurate appraisal of the effect of the drug on the brains could be determined. Similar comments were made regarding the quality of the slides of the eyes of these dogs. Dr. Kwapien also reported artifacts on 14 of 32 slides of the left eyes and 15 of 32 slides of the right eyes. In this study, 29 of 64 slides could not be reported on because of severe artifacts and 7 slides were missing.

In the same study poor staining was seen in some liver, bone marrow, spleen, lung, and mammary gland slides. Incomplete sections were noted for many slides of eyes, one intestine, and one pituitary. There were several sections missing; three of these were from tissues in which gross lesions were noted.

The poor quality of slides was pointed out by Hazleton in the draft reports submitted to Searle. Subsequently, a letter of February 5, 1971, from Dr. McConnell to Dr. Reno of Hazleton stated that, "The reports read very nicely." His response made no mention of Hazleton's comments on the quality of slides and there was no effort to prepare new slides to replace the missing or poor quality slides.

Pathology records were either not identified or were improperly identified

evaluation sheet did not contain information on the animal number, pathology number, identification of the person making the microscopic evaluation, or the date of the observations. Similarly, in the Norpace rat study it is not possible to identify who read the slides microscopically. In our investigation we could not determine who actually read the slides. Dr. McConnell, in an interview, would not commit himself to having read the slides although he believed he had written the pathology report.

Numerous deviations were found in reports containing tabulations of the number of tissues examined microscopically vis-a-vis the number reported to FDA. In the annotated report of the Aldactone 78 week rat study submitted to our investigators in October 1975, 34 different errors were noted concerning the number of tissues examined microscopically in only one table, Summary Table 11, of that submission. These errors were found in eye, pituitary, thyroid, adrenal, and other organs. Errors were evident in other tables as well.

Included in the report to FDA of the Aspartame hamster study is the report of slides of several organs of one animal for which our investigators determined that slides were never prepared. Similarly, in the Norpace dog study, there are discrepancies between what the firm reported to FDA regarding the number of slides of tissues read and what the investigators found regarding the numbers of slides actually read. In the Aspartame 104 week rat study conducted at Hazleton, 5 animals were described as having tumors in the histopathological incidence table. A check of the slides and blocks

in Hazleton's pathology department reveals that neither were present for the tissues in which the observations were made. Also at Hazleton, positive findings were reported by pathologists on 15 slides of this study but no record could be found that slides were ever made of these tissues. Since the investigation, Hazleton has attempted to determine the source of these errors relating to the tumor slides. The Task Force has received no report of Hazleton's findings.

Part of the difficulty in attempting to identify precisely what tissues have been examined and what tissues have been reported to FDA and to make a reasonable assessment of what happened in the conduct of the study, results from the lack of "original" postmortem work sheets or documents. Such instances include the Aspartame 115 week and 104 week rat studies; the Norpace 40 week rat study; the Syncro-Mate studies; and the Flagyl 80 week study.

An example of one occurrence which demonstrates the inadequacy of control between gross pathology and histopathology at Searle is available in a description of animal K23CF in the 115 week Aspartame (DKP) rat study. This animal, a control female, was reported on gross necropsy as having a tissue mass of approximately 10 x 8 x 3 cm in the left inguinal region. A notation, in a different handwriting, made at the bottom of this gross observation records states, "no mass found in bottle". In the microscopic findings of this study the mammary gland is reported as having a "necrotizing cystadenocarcinoma; well differentiated." Dr. Stejskal was asked how

it would be possible for this mass to have been read microscopically when the technician responsible for preparing the slides indicated that the mass was not contained in the specimen bottle. The investigators inquired as to whether it would have been possible that the tissue mass was in another specimen bottle. The pathologist's response, as reported by the investigators, was that, at the time the animals were sacrificed, "you should have seen things when this study was run--there were five studies being run at one time--things were a mess!"

Reproduction and Teratology Studies

Because of the serious consequences of teratogenicity, assessment of the potential of a test substance on reproductive and developmental processes constitutes an extremely important phase in safety evaluation. The rapid rate of change in morphological, biochemical and physiological properties of the conceptus, the embryo, and the neonate presents special problems. Important considerations are selection of appropriate species, and absorption of test substance. The planning, performance and evaluation in this sphere requires a high degree of sophistication.

The person responsible for most of the reproduction studies reviewed was apparently inexperienced in conducting studies of this nature and yet was given full responsibility at Searle with a title of Senior Research Assistant in teratology. His prior experience was one year's employment with the Illinois Wildlife Service where his work involved population

dynamics of the cotton tail rabbit. When asked by the investigators during an interview what qualifications or training he had for conducting reproduction and teratology studies, he replied that shortly after his employment he went to a meeting of the Teratology Society and Searle provided him with any books on the subject he wanted. This individual was also responsible for the training and supervison of a research assistant and two technicians.

Protocols were not available for four of the five Flagyl reproduction studies so it was not possible to determine whether they were or were not followed.

In the rabbit reproduction and teratology studies, Flagyl was administered buccally in a corn oil suspension. Information provided to the investigators by the Metabolism Group at Searle concerning the bioavailability of Flagyl indicates that buccal administration may be valid and would permit reproducible results if absorption was complete. However, the insolubility of Flagyl in corn oil (2 mg/ml) and the concentrations needed for this particular study brings into question the validity of this mode of administration for this experiment. The insolubility of the drug in corn oil permitted rapid settling and Searle technicians reported substantial leakage of the administered drug from the buccal cavity with residual test substance found on the lips and mouth parts of the dosed animals. It is therefore not possible to determine the actual dosage the animals received.

Further, while the protocol for this study called for administration of concentrations of 2% and 5%, and our calculations indicate that these concentrations were actually prepared, the report to FDA states that concentrations of 2% and 10% were administered, thus showing the drug in a more favorable light.

In the three rat reproduction studies, there were incomplete records and reporting discrepancies including inaccurate reporting of average maternal body weight, animals dropped from one study without explanation, mating observations unrecorded, and autopsy records not maintained.

Review of 5 reproduction and teratology studies for Aspartame revealed poor animal husbandry practices and problems in the design of some of the studies. In a memorandum of October 19, 1972, from a Searle technician to Dr. Rao, with copies to his superior and to Dr. McConnell, regarding the conception rate in the rabbit teratology study PT 1044S72, the author provided some possible reasons for the observed poor conception rate in the remaining animals following the death of 13 animals in this study. The memorandum includes statements regarding the poor physical condition of the animals when they were received by Searle, e.g., diarrhea; the lack of an adequate acclimatization perioo, e.g., 6 days instead of 3 weeks; breeding the animals before they were sexually mature, e.g.,

insemination at 96-116 days instead of 160-240 days and pseuodopregnancies because of injections of hormone. The memorandum concludes with this paragraph:

> "In view of the information that I have received, I feel the majority of the animals used for this study were sexually immature. Pseudo-pregnancy of some of the 27 rabbits may have also contributed to a lower conception rate. Some of these points were discussed at the beginning of this study, however we decided to go ahead as scheduled. Perhaps this information can be utilized in future teratology studies so that this type of problem will be eliminated."

A July 15, 1975 letter to Searle from one of its consultants on reproduction and teratology commented on the quality of the studies as follows: "...even following the track you did, it seems to me you have only confounded the issue by a series of studies most of which have severe design deficiencies or obvious lack of expertise in animal management. Because of the twin factors all the careful and detailed examination of fetuses, all the writing, summarization and resummarization is of little avail because of the shaky foundation."

Monitoring of Contractors by Searle

Three of the 25 studies which were reviewed during this investigation, were done totally for Searle by contractors; the 104 week rat studies for Aldactone and Aspartame at Hazleton Labs., and the 52 week monkey

study at the University of Wisconsin. Additionally, portions of other studies were done under contract, e.g., slides were read for Searle by MBR, Ltd. in the 78 week Aldactone study, the 106 week Aspartame dog study, the Cu-7 rat study, the 46 week Aspartame hamster study. Dr. Donald Willigan also read the slides of the Aldactone 78 week study, and Dr. Robert Kwapien, at Hazleton, read the slides of the 52 week dog study for Norpace. We conclude that Searle rarely monitored the performance of work done for it under contract.

In the 78 week Aldactone study slides read by Dr. Mauro were reread after they were returned to Searle by one of Searle's own pathologists. As far as we have been able to determine this is the only instance where Searle monitored the performance of MBR. It should be noted that MBR had read slides on at least 14 studies for Searle prior to the Aldactone 78 week study and there is no evidence that Searle ever monitored MBR's performance in these instances.

Searle characterized the 52 week monkey study by Dr. Waisman at the University of Wisconsin as first priority with the Searle Company, Yet, to the investigators, Searle disclaimed any direct control in the study, despite the facts that the protocol for the study was written by Dr. McConnell after Dr. Waisman initiated the study in January 1970; that frequent high-level communication took place between Searle executives and Dr. Waisman prior to and during the study; that Dr. Waisman was paid $15,000 by Searle for consultation on Aspartame; and that Searle provided

Dr. Waisman with 220 grams of Aspartame to ...

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While high-level communication between Searle management and Dr. Waisman, and knowledge of his activities (Waisman gave a seminar at Searle on his work in October 1970), is evident, there was virtually no effective monitoring of his work.

From what can be inferred from an interview with Dr. McConnell on October 14, 1975, he had serious reservations about the quality of the study, but he then went on to indicate that, in the absence of hard data to substantiate his reservations, there was no way to set them down in written form in a submission to FDA.

Inadequate monitoring or failure to monitor contractors by Searle is of interest because, according to Dr. Reno, Hazleton offers a client professional advice and consultation but then performs only those tests that the client asks it to do. As an example, when Hazleton did the histopathological evaluation of the dog brain and eye slides in the 52 week Norpace study, the report showed that many slides could not be evaluated because of artifacts, but Hazleton did not make new slides for evaluation even though Searle had supplied the tissue blocks and Hazleton had called attention to the poor quality of the slides in its draft report to Searle. In its investigation of this study, FDA asked Dr. Robert Kwapien of Hazleton if, in his opinion, an adequate evaluation could have been made using the slides supplied by Searle. He replied that he could only evaluate them with respect to the adequate slides (3) present, and that his summary so indicated this fact. The investigators

then asked him if he had been responsible for evaluating the study would additional slides have been requested. He replied that Hazleton is only a contract laboratory, and it was not its responsibility to make such a decision. Proper monitoring by Searle would have assured that new slides would have been made and read.

Data Analysis, Records, and Reports

During our investigation, we attempted to determine who collected data; how data were transmitted to the Math-Stat Department; who determined the appropriate statistical treatments to be employed; how analyses were made and summary tables and graphs prepared; how data were checked, both prior to and subsequent to statistical treatment; and the method in which reports were prepared, reviewed, and approved for submission to FDA. The Cu-7, Ovulen, and Norpace dog inspection reports contain detailed descriptions of the data, records, and reporting functions as they apply to those studies.

At each step of the sequence, numerous and substantial errors were found. In virtually every report of individual studies, there were discrepancies in "original" observations, use of statistic treatments which minimize differences among groups, errors in transcribing of data from one report form to another, etc..

Inaccurate Reports

Many Searle reports submitted to FDA have been characterized by a lack of continuity and perspective regarding the relationships to earlier reports on the same product. Each report appeared to be generated independently and not to receive critical review and evaluation to determine whether, when compared with earlier reports of the same study, there was consistency and an accurate reflection of the "raw data". Evidence of this conclusion is described in detail in the inspection reports of the Ovulen 7 year dog study, Norpace 52 week dog study, Flagyl 80 week rat study, and the Aldactone 78 week rat study.

Our investigation of the Ovulen 7 year dog study shows that preparation of the initial interim report for cycles 1 through 7, the Math-Stat Department did not use the laboratory data reported to it by the Path-Tox Department but instead went directly to the original spiral notebooks of raw data and in choosing values for calculations selected the improper numbers. These did not coincide with the values or averages reported by the Path-Tox Department, which our investigators found to be correct. In at least one instance the Math-Stat Department went to the original notebooks and entered the wrong animal identification numbers. The manner in which the data were recorded by the Path-Tox Department technicians was apparently in the random order in which the animals were housed. The manner in which the data were entered by the Math-Stat Department because they were either unaware of

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the randomness or chose to ignore it, destroyed that randomness and instead rank ordered the animals by treatment group and animal identification number. As a consequence, the values were entered in the wrong places and attributed to the wrong animals. Of significance is that no one at Searle adequately checked these data when they were returned from the Math-Stat Department, or these errors could have easily been detected.

The Ovulen study requires reporting to FDA at yearly intervals for seven years. The investigators reviewed the reports submitted for each of the annual reporting periods and found many errors in carrying data over from one report to the next. Some of these errors resulted in values being as much as ten times greater than they should have been. Once again, errors of this magnitude could have been found quickly with even a cursory review of these data by Searle personnel.

On June 28, 1971, Searle submitted the 52 week study of Norpace in dogs to IND 2861. The firm never submitted any revision or correction of this study to the IND nor did they indicate the existence of errors in this study. A "revised and expanded" version of this same study was submitted only in the NDA submission (17-447) of February 19, 1973. A supplement to this NDA dealing with the same study was submitted on June 18, 1973, which added a paragraph to that submission involving only changes in serum potassium levels. During our investigation it was noted that the 1973 submissions of the study corrected only a portion of the errors contained in the 1971 version. An example is Table 15,

which describes the number of slides made of a given tissue type, where the only corrections made were in the entries referring to brain and spinal cord; all other errors in this table remain uncorrected. The corrections on entries referring to the brain may well have been the result of FDA's request for reading of the low and mid-level dogs in January 1972 as described earlier in this report.

The 80 week study of Flagyl in rats was initiated in April 1966. The preliminary report of the results of this study was prepared by Dr. McConnell and submitted to FDA on October 31, 1969. The first full report was submitted August 3, 1970. A subsequent report was submitted in April 1974, which resulted from FDA's informing Searle on May 31, 1972, of discrepancies found in the 1970 version. Upon review of the April 1974 version, discrepancies were again noted, particularly with respect to changes regarding animal CM21 (described earlier). The nature of the changes made in this report precipitated the first visit to Searle by FDA, which has since resulted in this investigation. On October 23, 1975, a year and a half after they were advised of the discrepancies, Searle submitted another report to the FDA and provided a copy to the investigative teams. In a transmittal memorandum to FDA's lead investigator, Mr. Brodsky, Dr. William M. Merino, Director, Domestic Pharmaceutical Drug Products, Regulatory Affairs Department, of Searle referred to this version as the "Flagyl Annotated Report." The titles

of the four volumes of this report provide a clear indication of the number of variations of the same data which Searle had submitted to that date, and provide some hint as to the amount of FDA resources required to evaluate one set of data to reach a decision on the toxic potential of a drug.

Flagyl (SC-10295)

Eighty Week Chronic Oral Toxicity Study in the Rat

P-T 479S67

Amended Report

(1974)

Annotated Volume I

9/18/75

and

Corrected Volume I

10/17/75

Volume 1 of 4

Flagyl (SC-10295)

Eighty Week Chronic Oral Toxicity Study in the Rat

P-T 479S67

Amended Report

(1974)

Annotated Volume II

9/18/75

and

Corrected Volume II

10/17/75

Flagyl (SC-10295)

Eighty Week Chronic Oral Toxicity Study in the Rat

P-T 479S67

Volume III

Annotated

9/18/75

Volume 3 of 4

Flagyl (SC-10295)

Eighty Week Chronic Oral Toxicity Study in the Rat

P-T 479S67

Volume IV

Statistical Analysis

and

Individual Values

Volume 4 of 4

In a spot check, the investigators found numerous errors persisted in eight tables in Volumes I and II of the October 1975 version. The investigative team informed Searle of the existence of errors found in some of these tables.

On December 17, 1975, prior to their departure, the investigators received revised tables that had been recalculated and presumably

corrected. The investigators evaluated these tables and advised Searle before they departed, on December 19, 1975, that these tables still contained errors.

An example of some of the changes between these versions is in the charts summarizing histopathological findings. A chart summarizing these findings, prepared by one of the pathologists who examined the tissue slides in this study, was later changed to reflect different diagnoses for some tumors by a second pathologist after the first pathologist had left the company. Neither the original nor the revised chart included all the tumors found in the rats in this study. The revised chart was submitted to FDA as part of the preliminary report on tumors in the 1969 submission. The histopathology summary, Table 50, and the summary of tumor diagnosis, Table 58, submitted in the 1970 report of this study, were in conflict regarding the diagnosis of some tumors and neither included all of the tumors found.

The inspection report of the Flagyl 80 week rat study contains this statement, "We understood that Searle is currently in the process of making <u>additional</u> corrections in the report of this study, and another report will be forthcoming".

The final report of the 78 week Aldactone rat study was submitted by Searle on March 13, 1975. At the June 10, 1975 meeting of the

Cardio-Renal Drugs Advisory Committee, FDA personnel noted significant discrepancies in the data and their evaluation and interpretations by Searle and its consultants. Based upon FDA's own evaluation of that study, it was concluded that the drug has a positive carcinogenic potential. In August 1975, Searle submitted an additional analysis of tumors and submitted additional data of this study, including the previously unsubmitted pathology report by MBR. Subsequent to the time the investigation of this study began at Searle in October 1975, the investigation team was provided with three volumes dated September 18, 1975, which bear the following titles:

SC-9420: P-T 881

Corrected and Expanded

Volume 1

Annotated SC-9420

78 Week Oral Toxicological Study

In The Rat

Project No. 881

Volume II

Annotated Volume I

P/T 881

Aldactone

These appear as Exhibits 27, 28, and 29 of the inspection report of this study. In his letter of October 13, 1975, transmitting these volumes

to Dr. E. DeVaughn Belton, then Director, Division of Cardio-Renal Drug Products, Robert A. Moe, Ph.D., Senior Vice President for Scientific Affairs states:

> "These materials are not being presented as perfect or totally defect free. They are, however, in the most accurate form we could produce by extensive human effort. Further refinements may be identified that to date, have eluded this extensive review. As these develop, they will be incorporated into future submissions."

The first two volumes contain the results of a detailed review of the data of the 78 week study by Searle personnel. This review was carried out by a group of Searle scientists (non-toxicologists) for the purpose of identifying all of the differences between the initial report submitted to the FDA and actual raw data. The review identified differences which included: (1) transcriptional, clerical, and typing errors, (2) differences resulting from the use of different statistical treatment methods (geometric versus arithmetic means), (3) computer input errors and omissions, and (4) inclusion of additional data from reserve animals that were not incorporated as part of the original appendix to Volume I of the March 13, 1975 submission to the NDA. This report shows the original figures with strike-outs and corrected figures entered nearby. For example, Table 11 titled, "Tissues Examined Microscopically", shows 34 such changes. Table 15, titled "Histopathology Summary," contains 25

changes out of 152 entries under liver; 13 changes out of 72 entries under thyroid, 10 changes out of 36 entries under prostate, and 3 changes out of 48 entries under mammary gland.

Searle submitted the Corrected and Expanded Volumes I and II to its toxicologists who independently reviewed the data and prepared the third version of this report, "Annotated Volume I", also dated September 18, 1975. The review by the toxicologists was supposed to verify the results in the original report by comparing them to the data base appended to that report. Even in this report, the third version of the same data base, errors were noted including inconsistencies in the data among tables 15 and 16. Therefore, following three versions of the report, Searle still had inconsistencies and errors which FDA found.

During the preparation of the Task Force's report, Searle submitted yet another version of this study titled, "SC-9420:78 week oral toxicology study in the rat PT 881; Expanded Report dated March 2, 1976." The transmittal letter of March 2, 1976, signed by William M. Merino, Ph.D., comments on the status of the documents provided to the investigators in October 1975, as follows:

> "On October 13, 1975, an interim document entitled 'Annotated 78 week oral toxicology study in the rat, PT 881' (Volumes I, II, III) was submitted to the FDA investigational team on site at Searle at their request

and to the Division. This document was prepared as part of an intensive effort to provide a corrected submission to the Division and was not intended to be a final corrected report but rather only an interim working document."

It is a stinging indictment of Searle's lack of quality control of its data analysis and reporting that it concedes that it cannot guarantee the accuracy of its submission to FDA.

Selective Reporting

In three studies, the Aldactone 78 week rat study, the Flagyl 80 week rat study, and the Ovulen 7 year dog study, more than one pathologist read some of the slides.

In the Aldactone study, pathology reports were received by Searle from Dr. Jacqueline Mauro of MBR, Ltd. in 1973, and Dr. Donald A. Willigan in 1974. Between the readings of these two outside consultants, certain slides were also read by Dr. Stejskal, a Searle pathologist. Prior to this investigation, the only report submitted to FDA was that submitted to Searle by Dr. Willigan; the Mauro report was not provided to FDA until August 1975, and Dr. Stejskal's findings have never been submitted.

In the Flagyl 80 week rat study, slides of the 13 and 26 week sacrifice groups were read by Dr. McConnell prior to the employment of another pathologist, Dr. John W. Sagartz. Dr. McConnell also read the slides of other animals that died during the course of the 80 week study. Dr. Sagartz read the slides from the 52 and 80 week sacrifices and also read the slides of the 13 and 26 weeks sacrifices, which Dr. McConnell had previously read. Dr. Sagartz had Dr. McConnell's readings available when he read the slides. However, Searle submitted only Dr. Sagartz's report, which was generally more favorable to Flagyl. Examples include animal VM4, which Dr. McConnell reported as having an adenoma of the adrenal gland, while Dr. Sagartz reported a microcyst. Animal MM10, which was originally diagnosed as having a hepatocellular carcinoma by Dr. McConnell, was diagnosed as having a hepatoma (a benign tumor) by Dr. Sagartz. In this instance also, Dr. Sagartz' reading was submitted to FDA in the individual animal sheet, while Dr. McConnell's reading was included in the summary table of histopathological lesions in that same report.

In the Ovulen 7 year dog study, the slides were read by Dr. Smith for 5 animals, Dr. McConnell for 2 animals, and Dr. Hemm for 1 animal. For dog D13HF, the microscopic evaluation was performed by both Dr. Hemm and Dr. Smith; however, only Dr. Smith's evaluation was submitted to the FDA. His readings were considerably less detailed and informative than those of Dr. Hemm.

Problems of Data Management

In the Aspartame 46 weeks hamster study, blood samples reported in the submission to FDA as 26 week values were found by our investigators as being, in fact, values for different animals which were bled at the 38th week. Many of the animals for which these values were reported were dead at the 38th week.

In attempting to understand the entries in Table 8 of the Aspartame Food Additive Petition, which describes clinical chemistry values (Exhibit H-14 to the inspection report of the 46 week hamster study), the investigators interviewed Dr. K. S. Rao on November 11, 1975, and asked him to clarify certain BUN values found in that table. After reviewing the table from the submission and the original data from which the table was derived, Dr. Rao replied in writing stating:

> "It is apparent from the report, that the Appendix portion contains all the individual values of clinical lab data available from the raw data file. A selected portion of these values appears to have been used in computing group means. It is not clear what criteria may have been used for selecting a portion of data or for deleting the others in computing the means.
>
> For the above reason, I cannot compute the means for the BUN values indicated from the data available in the appendix portion of the report."

In the Aspartame 115 week rat study, the investigators point out data appearing on two tables, one in the raw data and the other in the submission to the FDA. It is impossible to determine how some of the values in the table in the submission were arrived at, although in two instances the submitted values appear to be an average of the two values shown in the raw data, and in the other cases, it appears that a single value was selected from the two values which appear in raw data. These findings appear on pages 10 and 11 of the inspection report of this study and in Exhibits R34 and R35.

In the March, 1975 submission of the Aldactone 78 week rat study, four malignant mammary tumors in treated females were omitted from the statistical analysis of the data. These tumors were reported in the data sheets submitted with the report and were found by FDA during our review of this study prior to the June 10, 1975 meeting of the Cardio-Renal Drugs Advisory Committee. During our investigation of this study, the investigators interviewed Dr. John Dutt, formerly manager, Mathematical/Statistical Services, who stated that he received the pathology report of Dr. Donald A. Willigan on January 21, 1975, and assigned the project of preparing a Sach's Life Table analysis to Mr. Li Chun Tao, a statistician. Mr. Tao informed the investigators that he requested the services of a clerk typist. According to Mr. Tao, the clerk typist assigned to him had never performed work involving preparation of computer field headings for Math-Stat before. He reported that he spent approximately 15-20 minutes explaining the task

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to her. Mr. Tao instructed her to work from Table 3 of Dr. Willigan's report, and to list each different tissue type according to the classifications "B" (benign) and "M" (malignant).

The clerk typist, on interview, stated she had been made aware of the differences in the designations "B" and "M" and she prepared the tabulation of tumor types under the benign and malignant categories on a sheet of lined, yellow paper, a copy of which appears as Exhibit 11 of the inspection report of this study. Her list omits any reference to malignant mammary tumors although four are listed in Table 3 of Willigan's report. Mr. Tao stated that while preparing the data for statistical evaluation he never reviewed the clerk's handwritten list of tumor types.

In order for the omission of the malignant mammary tumors to occur, the clerk had to fail to observe the presence of the malignant status of four separate entries which appeared on three separate pages of this table. Moreover, each of these entries would have had to be missed twice: once when the table of fields was prepared (Exhibit 11) and again when the tumor incidence data were entered (Exhibit 13). It must be noted that of approximately 10 different malignant tumor types contained in Dr. Willigan's table, only the mammary gland was omitted.

The investigators discussed this omission during a number of interviews with Searle representatives. Pages 27-34 of the inspection report of this study, describes a number of hypotheses advanced by Searle (including one by the company treasurer) to account for these omissions. None of the hypotheses, when tested, produced the same omissions and even the clerk herself, in making a new list from the Willigan data, could not duplicate her original list.

In the February 13, 1976 Supplementary Statement of Mr. Daniel C. Searle submitted for the record of the January 20, 1976 hearing before the Senate subcommittees he characterized this omission on a number of occasions as only a simple clerical error. Even if we accept the omission of these tumors as a simple clerical error, this procedure which forms the basis for the evaluation of whether this drug is carcinogenic or safe for use by vast numbers of patients in the treatment of chronic diseases, hinges on whether a single clerk makes or does not make, some kind of error. Verification procedures of inputs should be standard practice in any computer operation, yet this was clearly not carried out by Searle in this particular case. Our investigation shows this to be characteristic of Searle's practices in preparing submissions to FDA; concern is evidenced for form instead of substance and manifests itself frequently by submission of carefully edited and polished narratives accompanying poor quality backup data.

Epilogue

Evidence that the Task Force's findings are relevant to Searle's practices today is demonstrated by the receipt of a telephone call on February 23, 1976, by Mr. John Davitt of the Division of Anti-Infective Drug Products (HFD-140) from Mrs. Emanuela Dobrin, Manager-Scientific Liaison, Regulatory Affairs Department Searle Laboratories. The purpose of Mrs. Dobrin's call was to inform the Division that a heritable translocation (mutagenicity) study on Flagyl, begun in the fall of 1975, had been terminated prior to its completion when the following discrepancies were discovered:

1. There was a 28% error in dose calculation for the high dose mice (960 mg/kg vs. 750 mg/kg as called for in the protocol).

2. Prior to parturition, 18 of the female mice which had been mated to high dose males were killed by mistake. Apparently this error occurred as a result of caging these females on the same rack as males scheduled for sacrifice.

A follow-up letter of March 5, 1976, from Mrs. Dobrin contains none of the above details and the termination of this study is casually dismissed as a "failure to follow protocol".