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.