DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

OFFICE OF THE SECRETARY

ROCKVILLE MD. 20852

January 10, 1977

OFFICE OF THE GENERAL COUNSEL

Honorable Samuel K. Skinner
United States Attorney
Northern District of Illinois
219 South Dearborn Street
Room 1500 South
Chicago, Illinois 60604

Dear Mr. Skinner:

We request that your office convene a Grand Jury investigation into apparent violations of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 331(e), and the False Reports to the Government Act, 18 U.S.C. 1001, by G. D. Searle and Company and three of its responsible officers for their willful and knowing failure to make reports to the Food and Drug Administration required by the Act, 21 U.S.C. 355(i), and for concealing material facts and making false statements in reports of animal studies conducted to establish the safety of the drug Aldactone and the food additive Aspartame. Concealing material facts relative to the Aldactone study also resulted in that drug being misbranded within the meaning of 21 U.S.C. 352(a) and 321(n), in violation of 21 U.S.C. 331(a).

I

The Statutory/Regulation Scheme

A. Investigational New Drugs. The Food and Drug Administration has responsibility for assuring that drugs marketed in this country are safe for their intended uses and are accurately labeled. The Federal Food, Drug, and Cosmetic Act prohibits the marketing of any "new drug" in interstate commerce unless a new drug application (NDA) filed pursuant to 21 U.S.C. 355 containing substantial evidence of the safety and effectiveness of the drug has been approved by the FDA. Before an NDA is approved for any particular use of a drug, that drug may lawfully be used only for investigational tests, first in animals and thereafter in humans. This testing is permitted only in accordance with 21 U.S.C. 355(i) and regulations promulgated thereunder.

The original statutory basis for regulating the investigational use of new drugs was provided in 1938 by the basic Federal Food, Drug, and Cosmetic Act. The Drug Amendments of 1962 authorized the FDA to establish by regulation new reporting requirements to assure that information about significant hazards, contraindications, side effects and adverse or unusual reactions associated with the investigational use of new drugs is disseminated rapidly. These regulations specify the form, content, and timeliness for the submission of such reports. Failure to comply with such requirements is prohibited under the Act, 21 U.S.C. 331(e).

A major purpose of the investigational drug regulations, 21 CFR Part 312, is to safeguard human subjects during the investigational phase of drug development. Accordingly, the regulations require that prior to the administration of any investigational drug to human subjects, the sponsor of the drug must file with the FDA a notice of claimed investigational exemption for a new drug (IND), which contains adequate information about preclinical (animal) investigations of the drug and any studies and other experience from which the sponsor has concluded that it is reasonably safe to initiate clinical (human) testing. A careful evaluation of the animal toxicity and pharmacological studies provides some assurance of the expected effects when the drug is administered to humans. If the data submitted in an IND justify the conclusion that the drug may safely be tested in humans, the FDA permits the sponsor to ship the drug to investigators. It is not uncommon, as is the case with Aldactone, that a drug may have an approved NDA for certain uses while simultaneously being tested in animals and/or humans for other uses under an IND.

Because the IND procedures provide a limited exemption for the distribution of a drug which has not as yet been shown to be safe and/or effective by adequate and well-controlled clinical investigations, the regulations require the sponsor to closely monitor the progress of pre-marketing investigations. The regulations provide that progress reports of such investigations be submitted to the FDA at reasonable intervals, not to exceed one year. 21 CFR 312.1(a)(5). In addition, the regulations require that a sponsor shall "promptly investigate" and report to the FDA "any findings associated with use of a drug that may suggest significant hazards, contraindications, side effects or precautions pertinent to the safety of the drug". If such a finding is "alarming", it must be reported "immediately" and clinical investigation discontinued or modified until the finding is adequately evaluated and a decision is reached that it is safe to proceed. 21 CFR 312.1(a)(6).

The results of drug testing are critical not only to establish the basic safety and effectiveness of the product, but also to identify possible side effects, contraindications, and the need for special warnings, all of which must be included in the drug labeling. The sponsor of every new drug submits proposed labeling for FDA approval at the time of initial marketing and thereafter to reflect new information resulting from its use.

B. Food Additive Petitions. The Act also provides for FDA approval of food additives. Approval of an additive is codified in a regulation prescribing conditions under which the additive may be safely used. The regulation is promulgated solely on the basis of a manufacturer's petition, filed pursuant to 21 U.S.C. 348(b), which contains reports of studies establishing the safety of the additive. As with investigational drugs, the FDA does not perform safety tests on food additives; it must rely upon the data developed by the petitioner. Studies supporting a petition are ordinarily performed only on animals; human testing is uncommon.

The major purpose of the food additive provisions, added to the Act in 1958, is to prevent the unrestricted marketing and consumption in human food of chemicals without reasonable proof that these chemicals will not adversely affect man, either immediately, over a life-time or in the next generation.

C. Monitoring Test Integrity. Reports of studies submitted to the FDA as part of INDs or NDAs and food additive petitions must be complete, balanced and truthful if the Agency is to fulfill its duty of assuring that these products are safe and that new drugs contain accurate labeling based on the result of preclinical and clinical testing.

The FDA has not routinely monitored the conduct of animal test results submitted in support of either new drugs or food additive petitions. The reliability of the testing is normally checked by FDA review of the sponsor's reports of the underlying raw data. If necessary, the FDA may review the underlying raw data itself in the possession of the sponsor. The FDA may also select manufacturers or preclinical testing laboratories for routine surveillance inspections. When there is reason to believe that there are irregularities or discrepancies in the conduct of tests or the reporting of test data, the FDA may conduct a compliance inspection in order to evaluate the testing facilities, practices, and record keeping

procedures to resolve any apparent discrepancy between the raw data and the report or to determine the truthfulness of data presented in the report.

Recent FDA experiences have identified significant problems in the manner in which many preclinical laboratory studies are performed. Deficiencies in the quality and integrity of reported data have prompted the Commissioner of Food and Drugs to establish a bioresearch monitoring program, and to propose the promulgation of good laboratory practices regulations which will delineate proper procedures for conducting preclinical laboratory studies. Congress has increased FDA's budget for the fiscal year 1977 by $16.6 million specifically to help achieve the goals of the new program.

II

The Searle Investigation

The genesis of the investigation of studies conducted by and for G. D. Searle was the FDA's discovery in 1972 of certain discrepancies in Searle data submitted in support of a large-selling anti-infective drug Flagyl. FDA review of the data was initiated because independent investigators had reported evidence that Flagyl was a carcinogen (an agent capable of producing cancer). Searle's own long-term toxicity study, submitted in 1970, had not concluded that Flagyl was a carcinogen. In April 1974, Searle submitted more studies on the issue of Flagyl's carcinogenicity and also submitted corrections to the data from its original long-term study. These corrected data raised further questions, resulting in FDA inspections initiated at Searle beginning in May 1974 and proceeding intermittently until the first of July 1975. These initial inspections failed to satisfactorily resolve questions of discrepancies and inadequacies in Searle preclinical testing and reporting of test results.

On July 23, 1975, Dr. Alexander M. Schmidt, then the Commissioner of Food and Drugs, established a special internal Task Force to review the conduct of animal experiments conducted by and for G. D. Searle and report to him. Inspections were conducted at Searle and at three independent laboratories, Hazelton Laboratories, Vienna, Virginia, The Wisconsin Regional Primate Center, Madison, Wisconsin, and Microscopy for Biological Research, Albany, New York, which had conducted or participated in the evaluation of animal studies for Searle.

The Task Force reviewed inspection reports covering 25 separate studies on seven different products, totaling approximately 500 pages plus 15,000 exhibits. Based on this information, data originally submitted by Searle, the scientific evaluation of animal tissue slides and other raw data, the Task Force issued its report to the Commissioner on March 24, 1976. A copy of the Task Force report was forwarded to the Consumer Affairs Section, Antitrust Division, Department of Justice, and to your office in April. Among other observations, the Task Force questioned Searle's handling of data applicable to the drug Aldactone and the reporting of studies on the food additive Aspartame.

The Task Force report was provided to Searle and the firm requested an opportunity to submit a written reply and to meet with the Commissioner to respond to the conclusions and recommendations of the Task Force. The meeting was held on May 18; Searle submitted its written reply to the Task Force report on May 21. I am enclosing a copy of the transcript of the May 18 meeting and the written reply of Searle to the Task Force report (Exs. 1a, 1b). At the meeting, Searle requested an opportunity to make further written reply to two memoranda by FDA pathologist M. Adrian Gross, a Task Force consultant who had reviewed much of the Searle preclinical testing data. This Searle reply was sent to the Agency on June 21, 1976.

III

Informal Administrative Hearing

After review in my office and in the office of the Associate Commissioner for Compliance of all the material relating to this matter, on September 3, 1976, the Agency issued, pursuant to 21 U.S.C. 335, a Notice of Hearing to G. D. Searle and Company, and [redacted] for apparent violations of the Federal Food, Drug, and Cosmetic Act and related violations of 18 U.S.C. 1001 concerning Aldactone and Aspartame. The hearing, originally scheduled for September 21, 1976, was postponed at the request of Searle until October 20. An amended Notice of Hearing, dated September 15, 1976, was issued to correct an inadvertent omission from the earlier notice and to verify October 20 as the hearing date. A copy of the Notice of Hearing was forwarded to the Consumer Affairs Section and to Assistant United States Attorney Fred Branding of your office.

At the October hearing, Searle submitted lengthy written replies to the 305 Not copies of these are enclosed (Exs. 2a-2e). In addition, Searle reiterated

a request for the Agency's investigational file covering the apparent violations which were the subject of the hearing. This request was denied, as was an earlier Searle request for "discovery" which referenced the Jencks Act, the Federal Rules of Criminal Procedure and Brady v. Maryland. Copies of correspondence concerning these requests have been provided to the Consumer Affairs Section and Mr. Branding.

As you know, preliminary reports of discrepancies in preclinical testing conducted by and for Searle were partially responsible for hearings on drug-related research held before 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 Kennedy on July 10, 1975. Subsequent testimony updating the investigation and the positions of the FDA and Searle were taken before the joint subcommittees on January 20 and April 8, 1976.

IV

Failure to Submit Safety Data on Aldactone

A. The Drug. Aldactone is a new drug marketed by Searle pursuant to NDA 12-151. The drug was first approved in 1960 for use as a diuretic (an agent that increases the secretion of urine) for congestive heart failure and for hyperaldosteronism, a relatively rare but severe disorder of the adrenal cortex often resulting in a marked increase in high blood pressure. By 1974, Aldactone and a related drug utilizing the same active ingredient, Aldactazide, constituted approximately [redacted] of Searle's total pharmaceutical sales, approximately [redacted] a year. Current sales are reported to be [redacted] a year.

In 1963, Searle submitted IND 714 to conduct studies to develop data for the use of Aldactone in massive doses in the treatment of myasthenia gravis (serious muscular paralysis). In 1969, Searle amended its IND to cover testing of Aldactone for severe congestive heart failure at dosage levels much higher than those approved in the NDA.

B. The MBR ("Mauro") Report. In 1970 Searle designed two 78-week toxicity studies in the rat on Aldactone, one to support the long-term use of the drug at dosage levels approved in the NDA and the other to support higher dose levels in the treatment of severe congestive heart failure. The first study, later extended to 104 weeks in duration, was conducted by Hazelton Laboratori

Vienna, Virginia; the second was performed by Searle in its own laboratories The study conducted at Searle began in August 1970 and rats were sacrificed and necropsied (autopsied) during February and March 1972.

In November 1972, consistent with prior practices, Searle submitted the slides of sections of organ tissues of the rats from the study it had performed to an outside consultant pathologist for examination. The slides were examined by Dr. Jacqueline Mauro, a board certified pathologist, at Micropsy for Biological Research, Ltd., Albany, New York (MBR). The repo of her "readings" -- the MBR report -- was submitted to Searle on March 21, 1973. In a letter to MBR dated June 1, 1973, Dr. [redacted] acknowled receipt of the report which "looks just fine" (Ex. 5).

In the summary of the MBR report, Dr. Mauro stated that her pathology review the data suggested a group relationship, meaning a drug-related or drug-induc relationship, with tumors (adenomas) of the testes and liver. She also noted a significant number of thyroid tumors and non-tumorous thyroid lesions which she called "adenomatous goiter". Dr. Mauro recommended that these findings be measured for statistical significance. A statistical review of pathology findings is important since an absolute cause-and-effect relationship usually cannot be established in experimental biology. Therefore, an association between an agent and an effect is determined as a probability. If the incidan of a toxic response, such as a lesion, is found among animals treated with th agent under study to a significant degree greater than in animals not exposed to the agent, the established practice is to regard the agent as responsible for that toxic reaction. Where, as here, the toxic reaction is the developme of tumors, it is likely to result in restrictive labeling imposed by FDA or even revocation of marketing approval.

C. Searle's Reaction to the MBR Report. In early August 1973, a statistical significant relationship between the administration of Aldactone and liver an testicular tumors, as well as thyroid tumors, was confirmed by Searle's Mathematics-Statistics Department based on the MBR report. Thereafter, at the request of [redacted], some of the liver tissue slides were reviewed by a then recently hired Searle pathologist Dr. Rudolf Stejskal He concluded that Dr. Mauro's analyses were "incorrect" and thus "unreliable" since certain slides which she had diagnosed as revealing benign tumors (adenomas) were, in his opinion, lesser lesions (hyperplasia) and that other slides that she had diagnosed as being benign tumors were in fact malignant tumors. On the basis of Dr. Stejskal's limited review of the liver slides, Searle did not submit the MBR report to the FDA.

In April or May 1974, Dr. Stejskal reviewed more of the slides which had been analyzed in the MBR report. This time, he felt that the slides revealed more thyroid tumors than had been reported by Dr. Mauro. Thus, while having concluded that her characterization of the liver slides was too extreme, he also found that her characterization of the thryoid lesions was too restrained (Ex. 4). In various interviews with FDA personnel and in written submissions to the Agency, Dr. Stejskal has never commented on the MBR diagnosis of testicular tumors which, according to Searle's Mathematics-Statistics Department, were, as Dr. Mauro suggested, drug-related and statistically significant.

In August 1974 -- sixteen months after it received the MBR report -- Searle sent the same slides examined by Dr. Mauro, and approximately 1,000 additional slides from the same study, to another contract pathologist, Dr. Donald A. Willigan. His report was received by Searle in December 1974. It reveals a statistically significant drug-related increase in tumors of the thyroid and testes, as did the MBR report, but most important to Searle, not tumors of the liver. The concern at Searle over the liver pathology of the MBR report must have been particularly acute; undoubtedly the firm recognized that this information would have to be included in the Aldactone labeling, with a probable decrease in sales. The production of tumors in the testes and thyroid of the test animals, at statistically significant levels, must also have been unwelcome news but, insofar as Aldactone is felt to be active in these endocrine glands, Searle was prepared to argue that these tumors would be less likely to concern the FDA and the prescribing physician. We disagree with Searle's discounting the tumors of endocrine glands. See infra at 14. However, the liver findings were more alarming because there was no theory upon which they could be discounted. Thus, unlike the MBR report, the Willigan report was submitted to FDA promptly upon receipt at Searle.

Immediately after the first Congressional hearings and the Commissioner's establishment of the Task Force, and immediately prior to the initiation of inspections by the FDA Task Force, which Searle had every reason to believe would include studies on Aldactone, Searle finally disclosed the MBR report to the FDA in July 1975, some 27 months after it had been received.

D. Violation of 21 U.S.C. 331(e) and 18 U.S.C. 1001. The FDA regards the MBR report as containing "alarming findings", namely, statistically significant drug-related tumors of the liver and also of the thyroid and the testes, especially given the wide use of the drug in humans. Accordingly, Searle was required to report these findings to the Agency "immediately" pursuant to 21 CFR 312.1(a)(6). If one were to conclude that these findings were not

"alarming", they unquestionably were of the type that suggested significant hazards, contraindications, effects and precautions pertinent to the safety of the drug and therefore should have been submitted to the Agency "promptly" as also required by 21 CFR 312.1(a)(6). Even if one took the view most favorable to Searle that these findings were neither alarming nor suggestive of significant precautions, they were significant and thus were required to be submitted to the Agency at least within one year of receipt by Searle. 21 CFR 312.1(a)(5).

The primary purpose of the requirement that test findings be submitted to th FDA promptly is to permit the Agency to assess for itself whether the investigational exemption should be modified or revoked. A manufacturer is not entitled to withhold damaging information in the hope that ultimately it might be proved incorrect. Moreover, the regulations do not preclude a manufacturer from filing expert criticism along with or following the reported study. In short, under any view of the facts, Searle was not entitled to discount the entire MBR report on the basis of Dr. Stejskal's review of some of the slides for only one of the tissue types. Moreover, to give great weight to Dr. Stejskal's analyses is to conclude that in May 1974 Searle had reason to believe, based upon his subsequent review of more of the slides, that administration of Aldactone in the study had caused even a greater number of thyroid tumors than reported by Dr. Mauro.

21 U.S.C. 331(e) prohibits the failure to make any report required by regulations under the IND provisions of the Act. The decision not to submit the MBR report was a conscious one and thus our Notice of Hearing charged this violation as an intentional act under the felony provisions of the Act, 21 U.S.C. 333(b). Failure to submit the MBR report also constitutes concealment of a material fact, a violation of 18 U.S.C. 1001.

E. Labeling of Aldactone: Violation of 21 U.S.C. 331(a). When in March 1975 the FDA received from Searle the report of Dr. Williqan which confirmed the statistically significant incidences of thyroid and testes tumors reporte to Searle two years earlier by Dr. Mauro, the Agency became concerned that the labeling for Aldactone was inadequate. On June 10, 1975, it convened the Cardio-Renal Advisory Committee, a group of non-FDA experts, to review the data then known on Aldactone. Even prior to the disclosure of the MBR report in July 1975, and based upon the result of the tissue slide examinatic by Dr. Williqan and the analysis at FDA's request of certain liver slides by Dr. John Boitnott, a pathologist at Johns Hopkins University, the Advisory Committee concluded that while the toxicological studies were incomplete they showed "definite and significant increases in neoplasia (tumors) of the thyroid gland, testes and possibly breasts and liver. They certainly warrant

a warning to the medical profession and a curtailment in the recommendations for use." A copy of the Committee's report is enclosed (Ex. 5). Aldactone has now been relabeled consistent with the Committee's views.

In view of the similar statistically significant thyroid and testes tumor findings in the MBR and Milligan reports, and the findings of liver lesions by both pathologists, we believe Searle's failure to submit the MBR report resulted in violation of 21 U.S.C. 331(a) for causing the shipment in interstate commerce of Aldactone which was misbranded within the meaning of 21 U.S.C. 352(a) and 321(n) in that its labeling did not reveal the potential of the drug to cause tumors, a potential disclosed by the MBR report. As you can see, the Advisory Committee's conclusion also supports FDA's view that the findings in the MBR report were "alarming".

V

Analysis of Searle's Explanations
for Failure to Submit the MBR Report

The administrative process, including the special Task Force and the 305 Notice and hearing, has been extensive; much of the dialogue between Searle and the FDA involves complex issues. The following portion of this letter, as well as parallel discussions of apparent violations involving Aspartame, must necessarily be specific in order to comprehensively and accurately reflect the context of this case. Regrettably, the length of this letter bespeaks our goal.

Searle's explanation for its failure to submit the MBR report, set forth in various documents, is best summarized in the firm's response to the Notice of Hearing which was submitted to the FDA on October 20, 1976. Without attempting to provide at this time a point-by-point critique of the Searle submission, comment upon the main recurrent themes provided in Searle's defense may be useful.

1. From the beginning, Searle has repeatedly taken the position that the MBR report was "proven" by its own pathologist to be "incorrect" and thus Searle was under no obligation to submit it to the Government.

Searle's contention that Dr. Mauro's pathology results were unreliable must be evaluated in light of the fact that pathology is a judgmental discipline. Proliferative lesions of the liver cells can be subclassified according to the particular nature of the proliferation. A diffuse

increase in hepatocellular elements is usually termed "diffuse hyperplasia" or simply, "hyperplasia". When such proliferation is not diffuse but rathe a spotty distribution throughout the tissues with islands or zones of proliferating cells, the term "nodular hyperplasia" is utilized. When such nodules of hyperplasia contain cells which the pathologist deems as having been permanently altered or "transformed" into neoplastic or tumor cells, the term "neoplastic nodule" is applied; this is taken to represent a group of proliferating cells which have "crossed the boundary" on the way to becoming a liver tumor. Various pathologists utilize other recognized terms such as "adenoma" to signify a benign liver tumor. A tissue slide characterized by one pathologist as an "adenoma" would also meet the criteri for "neoplastic nodule". The most extreme form of cellular proliferative stage, the malignant tumor variety, is commonly termed "hepatocellular carcinoma".

What is important, however, is that all these various terms represent a series of characterizations of stages of the proliferative process which can be viewed as a continuum. It is entirely possible that two pathologists may examine a given lesion and characterize it somewhat differently. This does not necessarily mean that one is "right" and the other is "wrong". Therefore, one must examine characterizations of liver alterations in a set of animals and ask whether a pathogenic process, such as a proliferative change, is evident.

Accordingly, it is proper to focus on the <u>similarities</u> among pathologists rather than emphasize the differences among them. When Dr. Mauro refers to "adenomas" and Drs. Stejskal and Willigan reference "nodular hyperplasia" and Dr. Robert Squire, a cancer expert at the National Institutes of Health who reviewed some of the liver slides at the request of the FDA Task Force, talks about "neoplastic nodule", each one is calling attention to a proliferative change in the liver. One may grade such a proliferation along the continuum or by different phrases from another one, but basically they imply the same problem. The proclivity of experts to use different terms in liver pathology was recently demonstrated at a workshop at the National Cancer Institute published in "Cancer Research", Vol. 35, Nov. 1975, copy enclosed (Ex. 6).

Searle also alleges "extreme variation and contraindications in diagnosis" between Drs. Stejskal and Willigan on the one hand and Dr. Mauro on the other. FDA believes that the differences in diagnoses were not extreme and reflect merely the continuum of diagnostic evaluations of the same class that are well recognized in the field of pathology.

2. Searle argues that the IND regulations presuppose that the data which must be submitted must be accurate and reliable. 305 Reply, pages 10, 15. 21 CFR 312.1(a)(6) refers only to "findings" which are significant or alarming. Accuracy is not used as a standard precisely because such findings at this preliminary stage may, in many cases, be undermined. By contrast, the requirement to submit progress reports within a year does state that they be "accurate", reflecting the Agency expectation that by then any discrepancies will have been resolved.

Searle argues that the applicable statute and regulations do not require reports of all animal studies conducted during the course of clinical investigations but only reports of testing on humans and of those animal tests conducted before human testing is initiated. In addition, Searle contends that the IND regulations are unreasonably ambiguous. 305 Reply, pages 16-21. These arguments are without merit.

In the interest of protecting patients taking experimental drugs, the statute authorizes regulations requiring the reporting of animal tests before tests on humans are allowed. However, the regulations also permit so-called Phase I and Phase II clinical (human) trials to proceed before all the preclinical (animal) work is concluded. Accordingly, it is not uncommon that long-term animal studies, such as the 78-week Aldactone study, are undertaken concurrently with initial human testing. Item 10a of the form for the "Notice of Claimed Investigational Exemption for New Drugs" notes that these first two phases "may overlap and, when indicated, may require additional animal data before these phases may be completed or Phase III may be undertaken". 21 CFR 312.1(a)(2). The regulations therefore contemplate additional animal studies during testing in humans.

Searle also seems to rely on the phrase "such investigational use" in subsection 3 of the IND statutory provision, arguing that this refers to human test results only. This is incorrect. The results referred to in subsection 3 are those, as the statute goes on to state, "as the Secretary [by delegation, the Commissioner] finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of [a new drug application]". Thus, reports must be submitted to the Commissioner to permit him to determine whether the subsequent new drug application will be approved or denied. 21 U.S.C. 355(b) provides that NDAs must contain full reports of "investigations" which have been made to show whether or not a drug is safe for use. There is no distinction

between clinical and preclinical investigations; the statutory phrase includ both. Indeed, a new drug application may not be approved unless "substantia evidence" is submitted in support of the safety and effectiveness of the dru Substantial evidence is defined in the Act, 21 U.S.C. 355(d), as evidence consisting of "adequate and well controlled investigations, including clinical investigations". Obviously, the Act presupposes that reports will be submitted of preclinical investigations, otherwise the specific reference to "clinical investigations" would be meaningless.

Searle argues that the use of the term "investigators" in the regulations necessarily means investigators involved in clinical investigation. This is not true and the regulations do not use that phraseology. If anything, the regulations make clear that where clinical investigations are meant to be specified, that phrase is used.

Searle further argues that the MER report cannot be considered a "finding" under the regulations identified by the charge. There can be no question that the readings of a pathologist of tissue slides are "findings" in preclinical tests; the results of an entire study are usually stated in terms of the tissue slide pathology. If anything, the use of the word "findings" in the regulations suggests that information must be submitted to the Agency whether or not it can be considered, of itself, a completed or final "report".

3. Searle notes that the 78-week rat study in question used much higher dose levels than would be the usual human daily dose and thus the tumor findings were neither alarming nor even significant in terms of safety. 305 Reply, page 1. Most investigational toxicity studies in animals involve massive doses of the drug being tested.

The reason for the use of large doses of a drug in test animals is that such tests are designed to identify toxic reactions in those portions of the user population who are most susceptible to the drug. Accordingly, to accentuate the effects and maximize the probability that adverse reactions will become manifest, the relatively small number of test animals are given large doses. In fact, because the purpose of a preclinical toxicity study is to determine a toxicological profile of a drug, the human dose is an almost meaningless comparative measure. In animal studies, the question is what reactions will be manifested, not how much can the animal tolerate.

Even if the comparison were valid, the level of the animal dose as compared to the human dose is misleadingly referenced by Searle. The animal study in question was designed specifically to establish human use for the treatment

of severe congestive heart failure at dosage levels four to six times larger than the human dose for which the drug is marketed. Moreover, while comparing the animal test dose to the dosage for human use, Searle fails to acknowledge that at the time of this animal study, it was testing Aldactone in humans at six times the dosage of the drug then approved. In its written reply to the 305 Notice, Searle also emphasizes the lack of significant findings from the study done at Hazelton which was completed on Aldactone at approximately the same time as Searle's own study. 305 Reply, pages 2-3. The Hazelton study, however, does not balance the Searle study since, among other reasons, the amount of Aldactone received by the highest dosed animals in the Hazelton study was an amount between the low and mid-doses for the Searle test animals.

4. Searle contends that the MBR report was incomplete. 305 Reply, page 9. However, the report, as received by Searle and ultimately submitted to the Agency, is in precisely the same form as other pathology reports by Dr. Mauro that Searle unhesitatingly submitted to the FDA. In fact, Searle itself was capable of "completing" the study by adding to Dr. Mauro's pathology examination the statistical analysis it had performed in August 1973 and the gross observations from the necropsy. Searle chose not to do so.

5. Searle also insists that Dr. Williqan's diagnosis were more unfavorable to the drug and thus Searle cannot be accused of hiding "damaging" informatic 305 Reply, page 8. This assertion is very misleading. Dr. Williqan's diagnc were unfavorable in the same respect (thyroid and testes) as Dr. Mauro's reports were unfavorable; his diagnosis simply made bad news worse. The real significance of Dr. Williqan's diagnosis is that he did not find a statistica significant incidence of liver tumors, which was Searle's greatest concern with the MBR report and was the reason why Dr. Stejskal was asked in August 1973 to initially review the liver slides, not all slides.. It should also be noted that until May 1974, when Dr. Stejskal reviewed not only liver slides but numbers of the thyroid and testes slides, the only basis upon which Searle could conclude that the entire MBR report was unreliable was Dr. Stejskal's review of some of the liver slides from the high dose and control groups. Dr. Mauro, on the other hand, looked at approximately 5,000 slides, including 277 liver slides. But even the refutation of Searle' argument tends to obscure the point: The IND regulations are designed to fur data to the FDA before it is re-evaluated, whether the result be to confirm or undermine the initial conclusions.

In a similar vein, Searle also discounts the admittedly unfavorable thyroid and testes diagnosis on the ground that these are endocrine glands and were the "expected" site of drug-related reactions since Aldactone is felt to be an endocrine-active drug. 305 Reply, page 21. This "target-organ" argument is unsupportable.

Even assuming that a drug acts where it is "expected" to act, the nature of the reaction is not predictable. That is why animal toxicity studies are conducted; to determine the range and severity of reactions. There were many abnormalities in the "target organs" of the rats on this study. A tumor is one of many reactions; but it is one of the most serious kinds of toxic reactions that are seen. Moreover, animal toxicity studies are regulatory submitted to the FDA which reveal little or no significant toxic reactions, even in those organs theorized or "expected" as being the "target organs". Because every agent known to cause tumors in man also causes tumors in animals, tumors in animals constitute alarming implications for human toxic reactions.

FDA has required Searle and other manufacturers of oral contraceptives, which are endocrine-active compounds, to conduct long-term animal toxicity tests. When tumors of the mammary gland, one of the endocrine glands, are discovered, the FDA has forced the removal of the particular drug from the market and prevented testing in humans. With the oral contraceptives, all of which have basically the same therapeutic action, some have caused tumors in test animals, others have not. Obviously, therefore, "target-organ" tumors are not predictive.

16. Searle justifies its failure to submit the MBR report based in part on Dr. Mauro's use of terminology in evaluating the thyroid slides, arguing that her choice of words bespeaks Dr. Mauro's unreliability as a pathologist 30f Reply, pages 11-12. Dr. Stejskal has also stated that her terminology indicated that her report could not be relied upon.

What Dr. Mauro classified as an "adenomatous goiter", a non-tumorous hyperplasia of the thyroid, was classified by Dr. Willigan and Dr. Stejskal as an "adenoma", that is, a benign tumor. Searle never notified Dr. Mauro or MBR of any questions about Dr. Mauro's report, including its terminology. On June 1, 1973, [redacted] wrote to MBR stating that Searle had received the MBR report and that it "looks just fine". Searle now argues that this reference applies not to the liver or other readings themselves but rather to the form of the report.

Whether form includes terminology we can only speculate. The fact is that the term "adenomatous goiter" is recognized as a very precise reference to a non-tumorous condition of the thyroid probably resulting from a metabolic imbalance (Ex. 7, pertinent excerpts from recent editions of basic reference works in veterinary pathology). Thus, while Dr. Stejskal suggests Dr. Mauro analyses were overly general and thus unreliable, her slide readings appear

to have pin-pointed a significant distinction in thyroid proliferative lesions.

VI

Searle Reply to Allegation of Misbranding

Searle's reply to the allegations of causing Aldactone to be misbranded is essentially to accuse the FDA of not moving promptly in its role to review labeling. 305 Reply, pages 22-28. In fact, the Williqan report was submitted to FDA in March 1975; the Agency reviewed it and convened the Cardio-Renal Advisory Committee in June, which issued its conclusion in September. Also in September, Searle submitted proposed new labeling and thereafter a proposed "Dear Doctor" letter, both of which were inadequate By comparison, Searle's first proposed amended labeling for Aldactone came not immediately upon their receipt of the Williqan preliminary report in December 1974, nor upon the submission to the Agency of the final report in March 1975 but rather after submission in July 1975 of the MBR report and, notably, after creation of FDA's investigatory Task Force.

The burden to provide adequate labeling is placed by the law squarely on the shoulders of the manufacturer-proponent of a product. Moreover, in order to promptly advise physicians, FDA drug regulations provide that warnings and hazards may be added to drug labeling without prior approval by the Agency. 21 CFR 314.8(d)(1). Searle did nothing to react to the MBR report even after May 1974, when the thyroid tumor problem documented in that report was confirmed by Dr. Stejskal.

FDA, of course, did not have an opportunity to take action on Aldactone labeling on the basis of the MBR report until that report was submitted in mid-July 1975. Searle questions whether the labeling would have been changed on the basis of the MBR diagnosis alone, suggesting that it would not. To the contrary, with respect to thyroid and testes, the findings of the MBR and Williqan reports were consistent; the Williqan report identifying even more tumors than the suppressed report. If Searle had used the MBR report as received in March 1973, the labeling for Aldactone would have contained a statement — as it does today — about possible dose-related thyroid, testicular and liver consequences (Ex. 8). Contrary to the assertion in the 305 Reply, page 26, the FDA does not acknowledge that the MBR report is not the basis of the labeling change. The MBR report supports the labeling reference to liver lesions and, together with the Williqan report, substantiate the label warnings with respect to testicular and thyroid tumors.

VII

Summary

In sum, Searle received in March 1973 a pathology report which contained damaging information about its largest selling drug, information that was confirmed two months later by its own Mathematics-Statistics Department. A few of the slides which concerned Searle most, those concerning the liver, were reviewed by an in-house pathologist who took exception with some of the consultant pathologist's diagnoses. On that basis, the entire report, later confirmed by another pathologist to be substantially correct in its results, if not in its slide-by-slide analyses, was withheld from the FDA by Searle for over two years.

The legal as well as the practical answer to Searle's after-the-fact justifications for not submitting the MBR report is contained in Searle's own 305 reply at page 25: "The quality of the decision made must be judged by information available at the time, not by subsequent developments". Nowhere in its submissions to the FDA does Searle explain why it initially reviewed only the MBR liver diagnoses. Unquestionably, it was the report by its Mathematics-Statistics Department that, just as Dr. Mauro had suggested, there was a drug-related increase in liver tumors. This was the motivation for the withholding of the MBR report, the use of a second outside pathologis and the prompt submission of his findings even though they confirmed drug-related tumors in two other organs.

VIII

Concealing Material Facts and Making
False Statements in Studies Submitted
in Support of Searle's Food Additive
Petition for Aspartame

A. The Product. Aspartame is the trade name of a sweetening ingredient for food manufactured by Searle. Because Aspartame is a food additive, it may be marketed only upon FDA approval of a petition establishing its safety, which approval is codified as a regulation published in the Federal Register.

Aspartame is a synthetic product based upon two amino acids, l-aspartic acid and l-phenylalanine. It is intensely sweet, about 180 times as sweet as sugar, but is metabolized in the human body as a protein unlike sugar whic

is metabolized as a carbohydrate. Because of its great sweetness, Aspartame used in place of sugar would provide only approximately 1/180th of the calo of a quantity of sugar yielding equivalent sweetness. The potential commer value of Aspartame is enormous. Searle has built a manufacturing plant sole for the purpose of producing Aspartame.

B. Status of Aspartame. In the Federal Register of March 5, 1973 (38 F.R. 5921), copy enclosed (Ex. 9a), FDA gave notice that a petition had been filed by Searle proposing the issuance of a regulation to provide for the safe use of Aspartame in foods as a nutritive substance with sweetness and flavor enhancing properties. In the Federal Register of July 16, 1974 (39 F.R. 27137), copy enclosed (Ex. 9b), the Commissioner concluded that the evaluation of the data in the petition, which included approximately 150 studies and other relevant material, justified amending the food additive regulations to provide for the safe use of Aspartame under specified conditi

In response to this publication, FDA received objections to the regulation from members of the public and two requests for a hearing, provided under § 409 of the Act, 21 U.S.C. 348. Issues concerning the safety of Aspartame were identified by the objectors in the first part of 1975, and it was agreed that there would be an administrative hearing, called a Board of Inquiry. Based upon the Commissioner's conclusion in July 1975 that the integrity of certain animal studies conducted by Searle was questionable, and in conjunction with the establishment of the investigatory Task Force, including auditing of certain animal studies relating to Aspartame, the FDA stayed the effectiveness of the food additive regulation in a notice publishe in the Federal Register of December 5, 1975 (40 F.R. 56907), copy enclosed (Ex. 9c).

After the issuance of the Task Force report in March 1976, FDA began to consider methods by which certain of the studies submitted by Searle would be authenticated at Searle's expense, by a non-government panel of experts. This process, to be performed under a contract approved by the FDA and paid for by Searle, is soon to begin.

The 52-Week Toxicity Study in the Infant Monkey

A. Initiation and Basic Description of the Study. In November 1969, Searle officials decided it was "essential" to obtain the opinion of Dr. Harry A. Waisman about the differences and similarities in the side effects of Asparta as compared with those of phenylalanine (Ex. 10). Dr. Waisman was a leading

researcher associated with the University of Wisconsin Regional Primate Center and had published extensively on the toxicity of phenylalanine. Dr. Waisman's published works establish that phenylalanine is capable of producing brain damage in Rhesus monkeys. The Aspartame study was initiated on January 15, 1970 and terminated on or about April 25, 1971. Searle submitted its report to the FDA on October 10, 1972. A copy of the report of the study, excluding appendix tables, is enclosed (Ex. 11). Unfortunatel during the course of this study, in March 1971, Dr. Waisman died.

In this study, seven new-born Rhesus monkeys were placed on a diet which included Aspartame. The first infant monkeys became part of the study in January 1970; the last were added, at birth, in October 1970. The daily feeding of the monkeys, and monitoring and recording their actions, was the responsibility of Mr. Gunther Sheffler, a laboratory technician with a bachelors' degree who was selected by Dr. Waisman. The tables of laboratory test results, feeding schedules and the like which constitute the summary of raw data of the Searle report were prepared primarily by Mr. Sheffler. Presumably, Mr. Sheffler selected the new-borns for inclusion in the study; his selection was consistent with criteria which may have been set by Dr. Waisman. Although Dr. Waisman had access to and was undoubtedly familiar with the monkey colony at the Primate Center, in all likelihood he rarely if ever directly participated in the conduct of the study. However, he and Searle were responsible for the study design.

The Aspartame monkey study did not have "untreated concurrent controls", that there was no parallel group of new-born monkeys identified and monitored for comparative purposes which were not fed Aspartame. According to a Searle prc drafted several months after initiation of the study, the monkeys were to be kept on a diet with Aspartame for one year, then returned to a basal diet, subjected to behavioral and learning tests, and finally sacrificed and necropsied (autopsied) for the preparation of tissue slides to be reviewed microscopically for alteration (post-mortem work-up). Of the seven test monkeys, one died after 300 days; four were kept on Aspartame for approximate 365 days as planned; and administration of Aspartame for two others was cease on March 31, 1971, after approximately 200 days. No behavioral or learning tests were performed. Only the one monkey who had died during the test was necropsied and subject to post-mortem work-up.

B. Conflict Between the Study and Searle's Report of the Study. Before commenting briefly on the specific falsifications listed in the 305 Notice and to clarify why this study came to the attention of the Agency, you should note the very great literary license Searle officials took in drafting its

report. Searle has repeatedly contended that Dr. Waisman was working on his own, that Searle had little or no control over his activities, that the Searle protocol for this study was drafted after the inception of the study in order to attempt to bring some retrospective structure to the work done by Dr. Waisman and that because of Dr. Waisman's death, the documents reflecting the daily conduct of the study were in chaos. 305 Reply, pages 34, 37, 38, 43.

In essence, Searle now insists that the Waisman study was uncontrolled, and refers to it conspicuously as a "pilot" experiment; its shortcomings are itemized, all but enthusiastically.

Yet, while containing a few carefully couched disclaimers, the report of this toxicity study was submitted to the Agency just like any other of the 150 studies; it bears the authorship of the persons responsible for the study, namely, [redacted], and Waisman, in that order; it bears a Searle Pathology-Toxicology project number; it is in standard format setting forth methodology, observations, and the like, including a study design and conclusions.

Searle wanted data comparing Aspartame with phenylalanine. Dr. Waisman was the expert in the field and his name would carry great weight. The report to FDA is drafted in a manner which covers up the admitted inadequacy of the design, control and documentation of the study. However, when Searle is accused of representing this study for far more than it was, it denies almost all knowledge of or involvement with its initiation, design or performance; Searle cannot have it both ways.

Searle's conclusion that it had "no control over conduct of the study, and Dr. Waisman did not have to, nor did he, follow any suggestions by Searle or its employees" is difficult to understand. Searle documents in the possession of the FDA establish that in November 1969, Searle sought to involve Dr. Waisman in a study of Aspartame in order to compare its toxicity, particularly seizures and learning defects due to brain damage, with that of phenylalanine. See Ex. 10. In January 1970, such a study was initiated (Exs. 12, 13). It is also noteworthy that in a memorandum of a September 4, 1970, conversation with Dr. Waisman, [redacted] reports that he suggested to Dr. Waisman that two animals be placed on the study at lower dosage levels within the next few days (Ex. 14). This is exactly what

happened. Searle asserts that the behavioral testing was never anticipated on this "pilot" study but rather on a subsequent study which was being planned by an associate of Dr. Waisman. 305 Reply, page 36. However, various Searle documents obtained by the Task Force investigators, written both during the subsequent to the monkey study, establish beyond any question that behavioral testing, as well as the necessary post-mortem work-up, was originally planned for this study. See Exs. 11-14.

C. Specific False Statements or Concealed Facts. The 305 Notice delineates four false statements and entries in Searle's report of this study. (1) The report failed to reveal that the infant monkeys were not suitable for the study. (2) The report states that acceptable historical and contemporary data on untreated control monkeys were available, thus diminishing the necessity for concurrent control groups of monkeys. (3) The report falsely states that animals were not available for purchase and sacrifice (necropsy) at the termination of the administration of the test compound, as originally planned, because of personnel shortages. This statement also gives the misleading impression that the animals were incapable of being purchased when in fact they were available for purchase, although not immediately, after the test compound had ceased to be administered. (4) The report falsely states that necropsy data on one non-surviving monkey was lost to Searle due to "similar" reasons, namely, confusion and personnel shortages after Dr. Waisman's death. In fact, the data were available and were obtained at the Regional Primate Center by FDA investigators during the Task Force investigati Moreover, the monkey died approximately five months before Dr. Waisman's death

1. The first specific violation listed in the 305 Notice is based, in part, upon a January 19, 1972, memorandum written by [redacted] reflecting the reservations of Mr. Scheffler about the suitability and documentation of monke for the study (Ex. 15). [redacted] notes of a conversation with Mr. Scheffler state: "no extensive records on individual monkeys" (Ex. 16). In addition, on June 23, 1971, [redacted] was made aware of the fact that one of the seven monkeys on the study "never should have been included in your experiment since he had an obvious birth defect" (Ex. 17).

Searle asserts that neither nutritional nor reproductive histories of the mothers of the infant test monkeys were in any way significant to the study. 305 Reply, page 43. Nevertheless, the report states that only "infant Rhesus monkeys (Macaca mulatta) from full term, normal pregnancies" were used. In fact, the mothers were laboratory

monkeys and had been on other tests. The impact of the mother's health, nutrition, reproductive history, etc., would be significant were the mother to pass to her off-spring some deficiency, some altered type or rate of metabolism due to another chemical she had been exposed to previously, any or all of which might affect the infant monkey and its reaction to Aspartame. Further, these effects may be completely unnoticed by laboratory technicians.

2. The second specific allegation in the 305 Notice was that the report falsely states that a concurrent comparison control group (monkeys in the study that were monitored but not exposed to Aspartame) was unnecessary because acceptable historical and contemporary data on untreated monkeys were available. Searle admits that there were no existing post-mortem data from other monkeys in the colony but notes that there was such ante-mortem (pre-sacrifice) data for other monkeys. This seems to be correct. And in view of the fact that the study did not include behavioral and post-mortem aspects as originally planned, the non-existence of post-mortem data for untreated monkeys was rendered essentially irrelevant. Accordingly, this alleged falsehood now appears to have been adequately explained.

3. The third charge of falsification in the 305 Notice alleges that the reasons given by Searle for the failure to sacrifice and necropsy the monkeys "at the termination of administration of the test compound", namely, shortage of personnel and lack of supervision following Dr. Waisman's death, are untrue.

Searle's reply to these allegations focuses upon the fact that the monkeys were taken off Aspartame feeding allegedly without notice to Searle, and were thus "unavailable" for sacrifice "at the point of termination". The documents available to the FDA do not now establish that Searle had knowledge of the termination dates of administration of Aspartame (March 31, April 4 and April 25, 1971) until mid-June 1971. But the fact that the availability of these monkeys for purchase and sacrifice did not immediately coincide with the termination of the Aspartame feedings is not relevant; the protocol for this study originally provided for cessation of administration of Aspartame prior to sacrifice and necropsy. See Ex. 14. Thus, Searle's lack of immediate awareness of the termination of administration of Aspartame does not negate the fact that Searle later had the opportunity to buy the monkeys. Searle could not truthfully assert in its report to FDA that the monkeys were "unavailable"; so Searle stated that they were "unavailable at the time" when they were taken off Aspartame feeding.

Searle's failure to necropsy the animals, including examining brain tissue for those monkeys which had manifested seizures, is more likely based on the fact that Dr. Waisman had no post-mortem comparative data. If Searle had found adverse effects, it would have had no way to show that the consequences were not attributable to Aspartame. Searle did not want to take this chance. But Searle also did not want to admit the real reason for its indifference. The same apprehension of a "can of worms" is reflected in Searle memoranda discussing the potential consequences of Dr. Waisman's feeding of Aspartame to pregnant monkeys (Ex. 18).

Reliance upon alleged personnel shortages and lack of supervision do not explain why Searle did not closely monitor this study. FDA investigation did not reveal that things were plunged into chaos by Dr. Waisman's death as Searle has repeatedly suggested. 305 Reply, page 55. Treatment was continue for two to five weeks after Waisman's death on monkeys M-79 and M-14, complet their one year treatment as scheduled. During interviews in February of this year by FDA Task Force members, Mr. Scheffler stated that there were plenty of personnel on hand when Dr. Waisman died and that when the new laboratory director took over, he dismissed a number of employees because they were not needed.

Searle asserts that it makes no difference what reason is given for certain events as long as the events are true. We disagree. None of the real reasons for Searle's decision not to purchase the monkeys for post-mortem work-up was included in the submission to FDA; the monkeys were available for purchase and post-mortem work-up, but [redacted] advised [redacted], [redacted] and Saunders that the monkeys should not be purchased; they concurred. See Ex. 15. Nevertheless, it may be literally true that the monkeys were not known by Searle to be available "at the termination of administration of the test compound".

4. Finally, the report submitted to FDA states that necropsy data on the one non-surviving monkey, which received high doses of Aspartame and died after 300 days, were lost to Searle due to Dr. Waisman's death.

In fact, the data were available from the Primate Center and were obtained by the FDA Task Force investigators. The monkey died approximately five months before Dr. Waisman's death. Searle does not reply to this charge directly, but rather states that its use of the term "necropsy data" meant tissue slides, not the autopsy report dated October 22, 1970, which Searle claims it never received. It is undisputed that on October 21, 1970, Dr. [redacted] was made aware of the death of the monkey and that sacrifice was planned. Apparently, Searle failed to follow up on this information to determine that a report had been generated.

Searle now admits that it does not know what happened to the "necropsy data"; nevertheless, the report gives an answer as if the facts were known, namely, that the data were lost in the confusion after Dr. Waisman's death. This is an excuse based on no information, rather than the truth.

The 46-Week Toxicity Study in the Hamster

A. The Study. On April 20, 1970, Searle initiated what was to have been a 104-week toxicity study on Aspartame in the hamster. The study was terminated prematurely, after 46 weeks of treatment, due to an unexpectedly high mortality in both control and treated animals ascribed to a disease known as "wet tail" (severe diahrrea). Searle submitted its report to the Agency on December 8, 1972.

B. The Violation of Title 18. The alleged violation of Title 18, Section 1001, set forth in the FDA Notice of Hearing, is based on the following set of facts: Blood from certain animals in the study was collected for hematology testing and for blood chemistry at the scheduled 26-week interval. Samples were drawn and six different kinds of tests were conducted. Searle technicians appear to have experienced methodology problems with one of these, the test for serum glucose (blood sugar). Searle did not correct the problem with the glucose testing until approximately twelve weeks later. By that time, however, approximately 30 percent of the previously tested hamsters had died. Accordingly, at the 38th week of the study, other hamsters were taken as substitutes from the same feeding groups and blood was collected from them. The glucose values of these new animals were reported by Searle as being those of tests run at 26 weeks on blood samples from the original animals, which had since died. Thus, the glucose values represented for one set of animals at a particular point in time are the values obtained for different animals at a different time.

C. Searle's Inadequate Explanation. Searle admits the fact that its report contains this false information, 305 Reply, pages 66-67, but argues that this did not result from willful conduct or any intentional act. Moreover, Searle argues that this falsehood is not material to the appraisal of the safety of Aspartame.

Most Courts of Appeal have held that a violation under § 1001 can be sustained only upon a showing of the materiality of a falsehood. However, the courts generally define a "material" statement as one which has the tendency to influence or is capable of influencing. Actual reliance upon false information need not be shown. Nor must the Government prove that the person knew that a statement was false; rather, a reckless disregard for the truth or evidence of

a conscious purpose to avoid learning the truth will establish the requisite culpability. Here, documents in the possession of FDA establish at least that [redacted] knew of the need for a second glucose test and knew that hamsters were dying and substitutes were needed.

Searle suggests that these data were gathered and prepared by technicians reporting to Mr. Martinez, and that neither [redacted] nor [redacted] was aware of the existence of the problem concerning these data until they received FDA's Notice of Hearing. However, [redacted] admits in his 305 reply that he was involved in resolving the serum glucose problems, although he claims that he did not review this matter when drafting the report. [redacted] 305 Reply, page 17. The substitute animals were identified as substitutes on the raw data sheets which, we believe, [redacted], as the authors of this study, were obliged to review and may in fact have reviewed in order to attest to the integrity and accuracy of the report. Further evidence of disregard for the truth will have to be developed by the Grand Jury.

Searle argues that there was no motive for any intentional misrepresentation or concealing of the fact that glucose values for one animal were substituted for those of another. 305 Reply, pages 73-74. While the question of glucose levels seems to have been non-controversial in this study, the failure of the Searle report to simply note the substitution of test results could be attributed to the fact that at the time of the substitution the animals were contracting a disease and the study was accordingly threatened. Also, the reason for the wide variation in glucose values was, at first, not known. Until [redacted] confirmed that it was a laboratory problem, the unexpected test results might have been thought to indicate severe liver or pancreas reactions in the test animals.

It is true that these entries may not have been material to a determination of the ultimate safety of Aspartame. However, as Searle points out, numerous studies have been conducted and submitted to the Agency in support of the safety of this sweetening agent and thus, arguably, even a wholly fabricated study might not qualify as material in the sense of being a "but for" or independently sufficient basis for a decision.

We believe that the law permits prosecution for a falsehood that has the potentiality for influencing the Government in its evaluation of the immediate report in which the falsehood is contained whether or not the sum of the safety data is altered by the falsehood at issue. Moreover,

in this case, the hamster study was selected by the FDA Task Force as one of a few Aspartame studies for review upon the consultation with toxicologists in the FDA Bureau of Foods. Both this study and the monkey study met the criteria for selection of studies established by the Task Force.

Searle argues that the original records relating to the glucose substitutions are in existence and only their destruction or modification would be consistent with an intentional falsification in the final report. This, of course, is not a necessary prerequisite to a finding of intent; if it were, every defendant in every prosecution involving a crime of intent would argue, perversely, that his failure to destroy evidence of his culpability established his lack of intent.

One final note on both Aspartame studies. In considering the extent to which the reports were written to convey impressions more favorable than the underlying data would support, reference should be made to the memorandum of December 28, 1970, from Mr. Helling of Searle to, among others, Drs. [redacted], entitled "Food and Drug Sweetener Strategy", copy enclosed (Ex. 19). In that memorandum, Searle commits itself to obtaining favorable review by FDA personnel by seeking to develop in them a "subconscious spirit of participation" in the Searle studies. What FDA needs instead, and must have to evaluate products, are adequate and controlled studies, supported by the raw data, and reported accurately and in a timely fashion. The assumption that these reports can be relied on is at the heart of FDA's mission; the Agency cannot possibly look over the shoulder of each laboratory technician or draftsman involved in each of the thousands of animal and human drug studies conducted each year. The FDA must receive the truth, not psychological warfare. To emphasize the importance of safety data on Aspartame, we note that if ultimately approved for marketing, this sweetening agent can reasonably be expected to be part of the daily diet of every American.

IX

Individuals Who Appear to be Responsible for the Violations Charged in FDA's Notice of Hearing

A principal purpose for convening an investigatory Grand Jury would be to identify those persons responsible for any violations of the law investigated by the Agency. The persons named in the FDA 305 Notice

were identified on the basis of information known to or obtained by the Agency, but without the benefit of compulsory process. All Searle officers, employees, and former employees, were interviewed by Task Force investigators in the presence of Searle counsel or monitors.

A. Overall Corporate Organization. The organization charts and similar information available to the FDA reveal the following major outlines of responsibility within the Searle Company.

In 1971, T. B. Carney, Sr., was the Vice-President of Searle Laboratories for Research, Development and Control. [redacted] was then the Vice-President for Research and Development, under Mr. Carney. The research and development group consisted of six branches; Dr. [redacted] was the Director of Biology and was superior to [redacted] head of the pathology/toxicology section. In February 1972, [redacted] replaced Mr. Carney as the head of the RD&C and [redacted] became the Director for R&D. Dr. Francis J. Saunders replaced [redacted] as the head of Biology. The Director of Chemistry, a branch on equal level with Biology was Dr. Paul D. Klimstra. In April 1972, [redacted] became President of Searle Laboratories, a division of G. D. Searle and Company [redacted] was designated as Vice-President for Research and Development.

In July 1973, at about the time that Searle was beginning to deal with the MBR report, the research and development group was reorganized and Dr. Klimstra was made the Director, Pre-Clinical Research and Development, operating directly under [redacted] was made the Director of Pathology/Toxicology and reported directly to Dr. Klimstra. Dr. Saunders was given the title of Director, Research Liaison, at the same level as Dr. Klimstra, but outside the reporting chain of [redacted] Klimstra [redacted] In May 1974, [redacted] was given the title of Vice-President for Scientific Affairs although he continued to report to [redacted] and remained the immediate superior of Dr. Klimstra who in turn remained the immediate superior of [redacted] No other structural changes were made, and these designations remained the same through 1975.

B. Responsibility for Failure to Submit the MBR Report. When the MBR report was received at Searle in March 1973 it would have been within the immediate domain of [redacted], Director of the Pathology/Toxicology Department and his superior Dr. Saunders. From about the time that Searle

began its Mathematics/Statistical evaluation of the report (August 1973) until its submission, it would have remained within the jurisdiction of [redacted], who was then reporting to Dr. Klimstra. Dr. Stejskal, who originally reviewed the MBR tissue slide evaluations, was ultimately responsi to [redacted] through his immediate superior in the Pathology Laboratory. [redacted] functioned as head of the Toxicology Laboratory also reporting to [redacted]

1. Evidence of Responsibility Developed by the Task Force. The Agency has evidence that it was [redacted] who originally requested Dr. Stejskal to review the MBR liver slide analyses in July or early August 1973, and it was either [redacted] who requested further review of liver, thyroid, and testes slides in February 1974, which Dr. Stejskal performed in April or May of that year (Ex. 20). [redacted] were fully aware of Dr. Mauro's slide readings by September 1973. According to Dr. Dutt, the then head of Searle's Mathematics-Statistics Department, it was [redacted] who requested him to perform a statistical analysis on the MBR report in August 1973 (Ex. 21).

The FDA has no direct knowledge of the extent, if any, of personal knowledge or participation of Drs. Saunders, Klimstra, [redacted] in the decision to withhold the MBR report from the FDA. In view of the damaging effect of the liver findings, as well as the testes and thyroid tumors, and given the commercial importance of Aldactone in Searle's marketing line, it is difficul to believe that [redacted] did not advise his superiors Drs. Saunders (and thereafter Klimstra) [redacted] of the MBR report. Restrictive labeling for Aldactone, as in fact eventually resulted, would certainly have rendered these individuals accountable to their corporate superiors for any decline in sales of the drug. The evidence in our investigatory files leads us to the conclusion that [redacted] were in a position to know of th report and certainly had authority to decide not to submit it; we have howeve no direct evidence of their actual knowledge or participation in that decisio

2. The 305 Replies. In the Searle 305 reply, we are told that [redacted] promptly advised Dr. Klimstra of the findings of Dr. Willigan. 305 Reply, page 6. This does not necessarily mean that Dr. Klimstra was advised of the earlier Mauro findings, but it does raise the provocative question of whether Dr. Klimstra, Dr. Saunders and [redacted] were similarly advised when the MBR report was received in March 1973, particularly in view of the fact that Searle had no basis for discounting the MBR report until Dr. Stejskal's August review.

In [redacted] 305 reply, he states that he first learned of the existence of the MBR report on June 17, 1975, an assertion that is certainly appropriate for Grand Jury inquiry. [redacted], however, insists upon defending the institutional action of G. D. Searle and Company by arguing, at page 2 of his reply, that the MBR document was "preliminary and incomplete" since it "did not contain antemortem data, text or results of statistical analyses that are necessary for a final, complete and full report of the study".

This characterization of Dr. Mauro's pathology findings is nonsense. A pathologist's role in a study is to report examination of post-mortem lesions only; the contract pathologist never generates antemortem data or statistical analyses; the MBR report did not contain these and neither did the report from Dr. Williqan which was submitted to FDA. When a firm, such as Searle, receives a report from an outside pathologist, the firm itself provides the antemortem data and conducts statistical analysis. [redacted] further asserts that the MBR report lacks materiality. This is not true. The document was capable of and has influenced the Agency in its decision with respect to the labeling of Aldactone and in limiting human investigational studies.

[redacted] also claims ignorance of the MBR report until June 1975. He admits that he was aware that Dr. Williqan had diagnosed the slides from the 78-week study, but insists that he was unaware of any prior involvement in the study by Dr. Mauro. [redacted] asserts that [redacted] would not be expected to advise him of the results of pathology analysis on a routine basis. With certain minor exceptions, the response of [redacted] parallels that of [redacted] Apparently, neither [redacted] was required to authorize the re-evaluation of the slides for this study by Dr. Williqan.

[redacted] strongly asserts the corporate theory that the findings of Dr. Mauro were "so in error and so unreliable that the entire report was deemed untrustworthy"; that it was not a relevant part of the Searle Aldactone study, and in substance that it never was required to be submitted to the FDA. [redacted] 305 Reply, page 2. [redacted] assumes full responsibility for concluding that the MBR report was "fundamentally incapable of serving as a valid, defensible representation of the tumor data from the rat study involved". [redacted] 305 Reply, page 5. [redacted] claims he did not discuss the document with his superiors. [redacted] 305 Reply, page 7. Nevertheless, at page 11 of his reply, [redacted] states in the third person that "internal Searle records show that [redacted] regularly and candidly informed his superiors at G. D. Searle and Company of the toxicological status of company products, including recommendations relating to procedures and testing programs". While he claims he discounted in toto the MBR findings, [redacted] also states, at page 6 of his reply, that after Dr. Williqan's findings were reported he became concerned about human test subjects.

Accordingly, he discussed with Dr. Bernard M. Wagner, Professor of Pathology at Columbia University in New York the "question of tumors in thyroid, testes and liver." (Our emphasis).

C. Responsibility for False Statements in Reports of Studies on Aspartame. The 305 Notice with respect to Aspartame named [redacted] They were the authors of the reports that the FDA believes contain false information and/or omitted material facts. In our view, they are responsible for failing to report the substituted glucose values in the hamster study and are responsible for any false statements or concealed facts resulting from having drafted Dr. Waisman's "pilot" monkey study so that it would appear to be a valid, thorough scientific study.

X

Grand Jury Investigation Into Other Possible Offenses

The FDA Task Force investigated 25 studies involving seven products. Its report lists numerous incidences of poor laboratory practices, resulting in discrepancies and inadequacies in data in one or more of the investigational studies in support of each product. Some of these poor laboratory practices were characterized by the Task Force as "deliberate decisions" seemingly calculated by Searle to minimize discovery of toxicity and/or to allay FDA concern. Task Force Report, pages 4-5. The Task Force report also discusses examples of poor laboratory practices in animal studies submitted in support of the drug Flagyl, which were the subject of special attention at the Congressional hearings.

The Task Force report and each report of investigation for the 25 target studies have been reviewed by my office. Because the law does not make poor animal laboratory practices a punishable offense, much of the questionable conduct by Searle may not fairly be subject to a characterization, under the Act or Title 18, that will with reasonable probability establish a violation before a Judge or jury. For this reason, the scope of the Agency's 305 Notice was far more limited than the findings of the Task Force, whose investigation was designed primarily to review laboratory practices. Our selection of apparent violations for inclusion in the 305 Notice does not, of course, limit the inquiry of your office or by the Grand Jury.

One of the recommendations of the Task Force was that the FDA recommend to the Department of Justice that Grand Jury proceedings be instituted in the Northern District of Illinois using compulsory process in order to identify more particularly the nature of the violations and to identify all those responsible for such violations. Indeed, there are areas in which the Task Force investigation has raised serious questions that we believe your office should consider for presentation before the Grand Jury, but which were not included in the 305 Notice primarily on the ground that the notice is designed

to give persons an opportunity to respond to apparent violations of law which the Agency, on the basis of available evidence, intends to recommend for prosecution. The extent to which evidence was available to the Task Force reflects the fact that inspections began three months after the Task Force was created; Searle knew it was going to be audited.

Four decisions or courses of conduct by Searle were specifically considered by our office for Grand Jury review. These are set forth in the memoranda from Arthur Levine to me dated August 6 and 30, 1976, copies of which have previously been provided to the Consumer Affairs Section and to Mr. Branding. Two of these appear to us to be reasonably fruitful areas for Grand Jury investigation.

1. The Williqan report submitted to the Agency in March 1975 contained a computer print-out summary table of tumor findings which did not include four malignant mammary tumors in treated females which had in fact been diagnosed by Dr. Williqan and reported in his raw data. Searle explained the omission as the inadvertent error of a programmer in the Mathematics-Statistics Department who listed the mammary tumors as benign, although the raw data sheets she was using as a reference stated that they were malignant. These errors were not detected, or at least not corrected, by the supervisory statistician in that department or by Dr. Stejskal, the pathologist responsible for the study in the Pathology/Toxicology Department. Thus the Searle report, based on the pathology examination of Dr. Williqan contains, in part, false data.

All of the individuals involved in this episode have been interviewed by the FDA, and state, in essence, that they simply made an error. The FDA investigatory file does not now contain information which would establish a willfully false submission under Title 18. However, the drug industry generally and Searle particularly was concerned about evidence of malignant mammary tumors in test animals (Ex. 22). In order to accept the Searle explanation is to believe that the unfavorable mammary malignancy data were innocently omitted from the summary table four separate times by three different individuals. See August 6 memo., para. 2.

2. With respect to the discrepancies between the submission to FDA and the underlying raw data for the 80-week rat study on Flagyl, I concur in Mr. Levine's suspicions that [redacted] was asked to prepare for submission to the Agency an animal study which was poorly controlled and documented, and that he may well have known that the study contained inaccuracies or at least that the data was incomplete and could not be confirmed, but did not reveal these facts in the report of the study submitted to the FDA. See August 6 memo., pages 11-13.

Two other actions by Searle, discussed in paragraphs 3 and 5 of the August 6 memorandum and which are the subject of the August 30 amended memorandum, do not now appear to be fruitful matters for further investigation within the context of the Aldactone 78-week rat study. However, the general inadequacy of Searle statistical and sampling methods was admitted by Dr. Dutt, former head of the Mathematics-Statistics Department. See Ex. 21. The Grand Jury may wish to investigate consequences of these practices which, unlike the case with Aldactone, were not subsequently remedied. Moreover, Searle's theoretically conceivable but in fact inapplicable arguments over the specific facts pertaining to Aldactone demonstrate a willingness to rationalize in order to avoid admitting any error, even an error which turns out to benefit their product or further corroborates their procedures. See August 30 memo., para. 2.

XI

Procedure

The issues discussed in this transmittal letter as well as those raised by the Task Force report are based upon reports and supportive documents which amount to almost 20,000 pages. The Task Force report, Mr. Levine's memoranda of August 1976, and the Notice of Hearing focus these data into areas of potential criminal liability. It may not be necessary that each document be reviewed by your office in order to develop these matters for further investigation by the Grand Jury. However, Mr. Levine of our office (8-443-4360) and Mr. Carlton Sharp, a compliance officer in the Bureau of Drugs and Chairman of the Searle Task Force (8-443-1940), both of whom are intimately familiar with the facts of this case, would be pleased to provide any assistance in identifying particular documents in support of each charge in the Task Force report, the August memoranda, and the Notice of Hearing.

If you desire to review the exhibits and other significant data, such initial review might most efficiently be conducted in Rockville, Maryland, where the pertinent documents, together with Messrs. Levine, Sharp, and the other members of the Searle Task Force, are located. We would also be pleased to bring to Rockville, or to Chicago, at your request, the lead inspector for the Task Force, Mr. Philip Brodsky, and any or all others of the investigatory team. As issues are delineated and screened, Messrs. Levine and Sharp would be anxious to come to Chicago for whatever time necessary to continue discussions and preparation for the Grand Jury investigation.

I also request that you consider appointing Mr. Levine of our office a special prosecutor for the purpose of aiding the Grand Jury. In view of the breadth of the FDA investigation, the scientific matters raised, and the large volume of documents already assembled, his assistance would be extremely valuable. Moreover, such a procedure would eliminate any question, whether or not meritorious, that documents obtained by the Grand Jury may be shared only within the Department of Justice and not with the Food and Drug Administration.

As I mentioned previously, Mr. Fred Branding of your office has been kept fully advised of all pertinent developments in this case. Many of the attorneys in our office have had the privilege of working with him in cases recommended by our office. In his conversations with Mr. Levine over the last months, he has expressed a strong interest in this case and we would warmly support his designation as the attorney in your office responsible for reviewing the matter and handling the presentation to the Grand Jury.

As you know, this office cooperates closely with the Consumer Affairs Sectio in the prosecution of cases under the Act. A copy of this transmittal lette has been sent to Mr. Robert McConachie, Acting Chief. We anticipate that we will be apprised of your review of this transmittal and we and the Consum Affairs Section will appreciate being kept advised of any developments. Mr. Sharp has already identified many potential witnesses to support the patholo and toxicology principles that underlie the charges in the 305 Notice and th Task Force report.

We look forward to hearing from you following your initial review of these materials, and discussing with you a schedule for future action on this important and precedent-setting case.

Very truly yours,

Richard A. Merrill
Chief Counsel
Food and Drug Administration

Enclosures