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