Attachment 1 (3 pages) Folder 38

MEMORANDUM

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

DATE: Nov. 16 4th, 1976

TO : Mr. Carl Sharp

FROM : M. Adrian Gross

SUBJECT: Draft Agreement for Validation of Searle Aspartame Studies

The following are some comments which you requested on the document under reference as well as on the cover memorandum Wylie/Gardner dated November 1, 1976.

I must confess that I became deeply disturbed on reading this effort - last July 14th in a telephone conversation I had with Commissioner Schmidt during which I stated my reservations about this entire plan, he assured me that whatever is being contemplated in this area will be undertaken in full knowledge of and consultation with some of us who were intimately involved with the Searle investigation and that whatever is finally accepted will be of such nature as not to jeopardize or undermine all of our previous work. Given this kind of background I suffered a rude shock by the proposed plan in front of us at this time.

Let us put this matter in some perspective by establishing the basic facts here. The Searle investigation which started in the Fall of 1975 can be viewed as an investigation "for cause" following the discovery of certain improprieties in the conduct of animal studies during preliminary inspections in 1974 and in the first half of 1975. The report of the Task Force submitted in March 1976 in essence constituted a stinging indictment of Searle and it contained various recommendations for regulatory action including referral to the Justice Department for review of possible criminal violations of the law.

The Aspartame studies to which we have reference here are nothing but an extension of the studies which were reviewed by the Task Force. I see no essential difference between them and any of the studies already investigated. In the meantime this Agency has received a substantial amount of additional funding for the express purpose of monitoring the quality of research carried out by regulated industry in a much expanded fashion. As part of this program, there has been a marked degree of effort, time and money expended on setting up sundry task forces, steering committees, training courses for investigators, "surveillance" inspections, regulations for good laboratory practices, compliance programs, etc.

Yet, notwithstanding any of this, now that the Agency is confronted with the need of completing what it started out to do in this Searle matter, we seem to be turning to an outside group of questionable capability in this area:- the UAREP. I know absolutely nothing of the past experience of this outfit to carry out investigations of this sort - perhaps, whoever it was that selected this group to carry out our responsibilities for us might be as kind as to enlighten us on this point. I noted the name of Dr. Stowell associated with this organization - I have known Dr. Stowell for many years now from the time he was Scientific Director of the Armed Forces Institute of Pathology and I can readily agree that he has impeccable credentials and a remarkable achievement in his own field of pathology; as far as investigations of the sort that we are concerned with here, however, I would judge him to be a complete neophyte in this particular area. I also know nothing of the qualifications of the investigators which will be selected by Dr. Stowell or others at UAREP to do the actual "hands-on" part of the investigation - we need additional details here but I would doubt very much that UAREP could come up with a number of workers who are both experienced and competent in matters of this sort.

Speaking as a pathologist, I seriously question the wisdom of selecting a group of pathologists to oversee the kind of investigations that are called for here; pathology problems do not constitute but a small part of the difficulties involved in situations such as these. My own experience is that, as a rule, controversial technical aspects in pathology proper (such as whether any particular characterization of any given lesion is a proper one or not) are seldom an important factor in a determination whether any study contains serious flaws. This has been amply demonstrated in the extensive Searle investigation as well as in other investigations currently under way in the Bureau of Drugs. I have great difficulties in visualizing pathologists conducting a searching examination of a variety of records which have nothing to do with pathology or closely question a number of administrators, laboratory technicians or aids, animal caretakers, etc., on their practices, on details of their tasks, adequacy of their observations and so on.

I would not like to generate the impression here that scientific expertise in pathology or in any other scientific field associated with studies like these could or should be totally ignored. Far from it. However, the concept under which we have operated ever since I can remember is that investigations are best handled by trained and experienced investigators. Where there is a need to address certain scientific problems which transcend the capabilities of the investigators, the practice has always been for appropriately qualified specialists from the various Bureaus of the FDA to assist the investigators; in those few cases where outstanding technical difficulties beyond the capabilities of Agency scientists are required, we have not refrained in the past from using help from outside and I should hope we shall continue to do so in the future. But this help provided by scientists on an ad-hoc basis and only where it is required is an entirely different matter than having scientists <u>direct</u> the actual course of the investigation. While I believe it is entirely proper (in fact preferable) to have scientists <u>evaluate the scientific impact</u> of a set of findings, I cannot see professional scientists do the job of professional investigators any more than I could see members of a legal society doing the work of detectives or policemen in investigating various aspects of a specific crime.

It disturbs me to see from the draft we have here that the rôle of what is

termed the "FDA Monitor" will be reduced to little more than having this person be present during communications between UAREP and Searle; I find this kind of prospect ludicrous and I do not understand the need for it.

What I understand even less is why Searle should offer or be asked to pay the cost of this entire operation to the investigative agent in a direct manner; why is there a necessity for this body, UAREP, to enter into any kind of formal contract with Searle and why are we expected to co-sign such a contract ? The fact that Searle will pay for this cannot but give them some kind of decision-making role as is evident from merely reading the terms of this proposed contract. It seems to me that no-one except the FDA can have the responsibility for undertaking this kind of work - this is our mission and we are being paid from public funds to carry it out.

Although, as expressed above, there is much I do not understand about this entire plan, particularly its basic raison d'être, there is something here that I appreciate fully:- this is the statement at the top of page two of Wylie's memorandum:- "Searle understandably continues to press for the expediting of this agreement."

I would suggest that implementation of this contract can have only one of two predictable outcomes which are mutually exclusive:-

a) There are serious improprieties in the conduct of these studies. If this is the case, I would submit that inexperienced outside scientists selected by an outside agency under contract to the firm which is the object of the investigation, will have a markedly reduced probability of detecting such improprieties;

b) There are no serious improprieties in the conduct of these studies If this is the case, it would necessarily follow that any report written by the "investigators" would not signal the presence of any such improprieties. But, if so, for exactly the same reasons as listed above, such a report may well be interpreted as being nothing short of an improper whitewash.

My recommendation is simply that this entire plan be aborted forthwith, and that we proceed with this matter in the way we are supposed to; this is the way we have handled things like this in the past and the way we anticipate to operate in the future.

M. Adrian Gross
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