PRECLINICAL AND CLINICAL TESTING BY THE PHARMACEUTICAL INDUSTRY, 1977

HEARING

BEFORE THE

SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

OF THE

COMMITTEE ON HUMAN RESOURCES

UNITED STATES SENATE

NINETY-FIFTH CONGRESS

FIRST SESSION

ON

EXAMINATION OF THE PROCESS OF DRUG TESTING AND FDA'S ROLE IN THE REGULATION AND CONDITIONS UNDER WHICH SUCH TESTING IS CARRIED OUT

PART IV

MARCH 10, 1977

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THURSDAY, MARCH 10, 1977

U.S. SENATE,
SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH
OF THE COMMITTEE ON HUMAN RESOURCES,
Washington, D.C.

The subcommittee met, pursuant to notice, at 10:20 a.m., in room 2228, Dirksen Senate Office Building, Senator Edward M. Kennedy (chairman of the subcommittee) presiding.

Present: Senator Kennedy.

Committee staff present: Jay Cutler, minority counsel.

OPENING STATEMENT OF SENATOR KENNEDY

Senator KENNEDY. We will come to order.

The Food and Drug Administration is the guardian of the health of the American people. Each day every American ingests products with the potential to cause great harm. It is the solemn responsibility of the FDA to protect us from that harm.

In the last 2 years, the ability of that agency to fulfill its responsibilities has been called into serious question. Products which were already on the market and thought to be proven safe were placed under clouds of suspicion. The data which FDA had relied on and believed to be sound was shown to be seriously deficient.

Whether the problem was caused by sloppiness or negligence is less important than its consequences. In fact, millions of Americans were shown to be taking products whose safety had not been demonstrated. Perhaps most alarming was the admission that both the magnitude of the problem and the number of products involved was unknown. That is still the case today.

Millions of Americans are taking products—drugs, food, additives, food colorings—which they believe to be proven safe but which, in fact, have not been.

Our regulatory system is always supposed to give the benefit of the doubt to the American people. Drugs must be proven safe before they are marketed. Carcinogens must not be allowed on the American dinner tables.

But it is now clear that our regulatory system has broken down. It is hard to promptly remove an approved drug from the market even when the new information, had it been known originally, would have kept the product off the market in the first place. That is really the nub of the issue that we are facing here today.

The absence of the proof of safety does not mean that a product is harmful. But our system is designed to resolve uncertainties before marketing and not to learn of hazards at the expense of the health and lives of the American people.

We will explore several examples of this regulatory crisis today. We will look at widely used products which were approved as safe before marketing. We will see that the data on which they were judged safe are now considered inadequate. Thus, proof of safety is gone. But the products remain. The extent of risk to the health of the American people is unknown. But under our system they should not be asked to run this kind of risk at all.

The other example we will look at involves the use of the artificial sweetener, saccharin. New information has shown it to be an animal carcinogen. Federal law prohibits the appearance of carcinogens in the Nation's food supply.

This policy was vigorously supported by the past Director of the National Cancer Institute, Dr. Frank Rauscher, who urged that man's carcinogenic burden be reduced to the maximum extent feasible.

It is not yet known whether animal carcinogens automatically present hazards to humans. They may. They may not. But current Federal law is designed to minimize the risk to the American people while definitive answers are sought.

The public policy dilemmas are profound. Saccharin is not being immediately banned from the market. It may be a long time before it is removed. If it turns out to be a definite hazard to man, we will have exposed millions of people to it for an unjustifiable period of time while the regulatory process unfolds.

On the other hand, if it is banned immediately, and then is shown to be safe, it will have caused massive economic hardship, personal discomfort, and perhaps even medical risks to those citizens who need diet foods.

The question is, when you do not know, what do you do?

I believe the benefit of the doubt must always go to the American people. Each of us, our parents, our children, are exposed each day to many potential carcinogens. If we are not careful, if only one turns out to be harmful to us, then we will have unleashed a man-made cancer epidemic whose price we will pay for years to come.

Mr. Gardner, do you want to introduce your associates? They are all well known to this committee, but introduce them for the record.

We have two statements for the committee this morning, and maybe we will start off with the bio-test and then move to the other.

STATEMENT OF MR. SHERWIN GARDNER, ACTING COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, ACCOMPANIED BY DR. J. RICHARD CROUT, DIRECTOR, BUREAU OF DRUGS; JOSEPH P. HILE, ASSOCIATE COMMISSIONER FOR COMPLIANCE; JEROME A. HALPERIN, DEPUTY ASSOCIATE DIRECTOR FOR NEW DRUG EVALUATION (SCIENTFIC); DR. M. ADRIAN GROSS, D.V.M., BUREAU OF DRUGS; AND RICHARD A. MERRILL, CHIEF COUNSEL, FOOD AND DRUG ADMINISTRATION

Mr. GARDNER. Thank you, Senator.

On my far left is Mr. Paul Hile, Associate Commissioner for Compliance, Food and Drug Administration.

On my immediate left is Mr. Richard Merrill, Chief Counsel for the Food and Drug Administration.

Proceeding down the table to my immediate right is Dr. Richard Crout, Director of the Bureau of Drugs.

Seated next to him is Mr. Jerome Halperin, Deputy Associate Director for New Drug Evaluation, Bureau of Drugs.

On his right is Dr. Adrian Gross of the Bureau of Drugs.

Seated somewhat behind me and to my right is Mr. Forrest Patterson, who is Deputy Chief Counsel and is my advisor where separation of function requirements limit my participation.

I have also invited members of the Bureau of Foods to be present this morning in the event that their testimony will be needed to discuss issues that are raised during the course of the testimony. I will introduce them at the time their testimony is required.

As noted, we have supplied for the record two full and somewhat lengthy statements. I have a summarized statement of the Industrial Bio-Test Laboratories matter, and would also appreciate being able to quickly summarize in a general way the overall bioresearch monitoring program at the conclusion of the summary of industrial biotest, if that is acceptable.

Senator KENNEDY. Fine.

I have the 9-page statement. Is this the one you are going to read from?

Mr. GARDNER. I have a 4-page summary.

Senator KENNEDY. I have the 9-page statement and I am familiar with that. I had a chance to go over it. Maybe we should do that one.

Mr. GARDNER. Mr. Chairman, your staff has asked that we provide a status report on Industrial Bio-Test Laboratories (IBT), a large contract animal testing laboratory, which was mentioned in testimony given by Commissioner Schmidt at a hearing on July 19, 1976. Our inspections of this laboratory, since that time, has resulted in an important administrative action against the antiarthritic drug, naprosyn, and have called into question a study conducted on triclocarbon (TCC), an antimicrobial agent used in bar soap.

Additional investigations of other studies conducted by IBT are continuing at this time.

Senator KENNEDY. At the last hearing we looked into the Searle case and also the Biometrics case.

Could you give us a status of where they are now?

Mr. GARDNER. Could I ask Mr. Merrill to respond to that?

Senator KENNEDY. Surely.

Mr. MERRILL. Mr. Chairman, those two matters are both before the respective——

Senator KENNDEY. I cannot hear you.

Mr. MERRILL. Those two matters are before the respective U.S. attorneys, accompanied by recommendations from the Agency which we have previously provided to the committee.

I have been asked by the Department of Justice to limit our comments to that extent because those matters are still awaiting their consideration, and they are concerned about potential adverse publicity.

Senator KENNEDY. The status of the case is they are before the Justice Department for action?

Mr. MERRILL. That is correct.

Senator KENNEDY. Can you tell us what type of action?

Mr. MERRILL. The recommendations in each instance were for grand jury inquiry.

Senator KENNEDY. All right.

Let us proceed.

Mr. GARDNER. An inspection of Industrial Bio-Test Laboratories was conducted during the last week of June 1976 by Dr. Adrian Gross, Mr. Manfred Hein, a pharmacologist in the Bureau of Drugs' Division of Oncology and Radiopharmaceutical Drug Products, and an investigator from our Chicago District Office.

The inspection focused on a 22-month rat study on the drug naproxen marketed by Syntex under the name naprosyn. Naprosyn, NDS 17–581, had been approved for marketing in March 1976 for the treatment of arthritis.

Senator KENNEDY. This is a widely used drug for arthritic patients, is that correct?

Mr. GARDNER. That is my understanding.

Senator KENNEDY. Can you tell us how many elderly people used the product approximately?

Mr. GARDNER. I think Dr. Crout will be more familiar with those data than I.

Dr. CROUT. It will be in the many thousands at least. But I cannot be more firm than that. I just do not know.

Senator KENNEDY. Well, we are talking tens of thousands or hundreds of thousands, or a million?

Dr. CROUT. I am sorry, I do not know their distribution at this time. We can supply that. I just cannot give it to you off the top of my head.

[The information referred to and subsequently supplied follows:]

NDA 17-581

NAPROSYN® (naproxen) 250 mg. Tablets

QUANTITY DISTRIBUTED

June 1976 - August 1976

	Samples	Trade	Total
Bottles of 6	759,216		759,216
Bottles of 24	1,608		1,608
Bottles of 100	1,200	306,660	307,860

NDA 17-581

NAPROSYN® (naproxen) 250 mg. Tablets

QUANTITY DISTRIBUTED

September 1976 - November 1976

	Samples	Trade	Total
Bottles of 6	692,208		692,208
Bottles of 24	44,736		44,736
Bottles of 100	1,894	292,260	294,154
Bottles of 500		36,474	36,474

NDA 17-581

NAPROSYN® (naproxen) 250 mg. Tablets

QUANTITY DISTRIBUTED

December 1976 - February 1977

	Samples	Trade	Total
Bottles of 6	872,016	--	872,016
Bottles of 24	336	--	336
Bottles of 100	1,982	139,585	141,567
Bottles of 500	--	16,420	16,420

Senator KENNEDY. It is from common knowledge a commonly used drug?

Dr. CROUT. Quite widely used preparation.

Senator KENNEDY. Do we know how many Americans have arthritis?

Dr. CROUT. Again it is in the millions.

Senator KENNEDY. And the TCC, the other item that we are going to talk about here, this is an agent which is used in noncommercial bars of soap, is that correct?

Mr. GARDNER. That is correct.

It was widely put into use after hexachlorophene was banned for that purpose.

Senator KENNEDY. What sort of representative soaps have it?

Can you tell us what soaps have the TCC?

As I understand it, it is generally in all the deodorant soaps.

Dr. CROUT. Essentially all the deodorant soaps.

Senator KENNEDY. Do all the deodorant soaps have it or most of them?

I am trying to get the dimensions.

Dr. CROUT. It is the antimicrobial ingredient in soaps such as Safeguard, Dial, Zest.

Dr. GROSS. Safeguard.

Senator KENNEDY. The general deodorant soaps?

Dr. CROUT. The big brands. It is the most common ingredient in all the big brands.

Senator KENNEDY. All right.

Mr. GARDNER. I will return to Naprosyn.

The 22-month rat study appeared to be the only long-term carcinogenicity study carried out by or for Syntex on Naprosyn. Our investigators reported a number of serious problems regarding this study, including questions of animal identification, inadequate information on survival rates, missing original records, careless pathology operations, failure to report to Syntex and, therefore, to FDA, full information on the number of tumors observed in the study; failure to adhere to the study protocol, and other unacceptable practices.

Senator KENNEDY. Do I understand that the only long-term carcinogen study is unacceptable and that the drug is still on the market?

Mr. GARDNER. That is the Bureau's advice to me.

Senator KENNEDY. The answer is yes, is that correct? The answer to my question is yes?

Mr. GARDNER. To my knowledge, yes.

After an extensive evaluation of the findings of Dr. Gross and Mr. Hein, the Bureau of Drugs concluded that the deficiencies in the 22-month rat study were so serious that they compromised the scientific integrity of that study and rendered it unacceptable in reaching decisions regarding the long-term toxic potential of Naprosyn.

The decision reached by the Bureau of Drugs was that the serious errors and discrepancies in this study, which was material to the Bureau's decision to approve Naprosyn for marketing, constituted untrue statements in the application.

Section 505(e)(4) of the Federal Food, Drug, and Cosmetic Act requires that FDA withdraw approval of a new drug application (NDA), if it contains any untrue statement of material fact, whether or not that misstatement was knowing or even negligent.

Senator KENNEDY. In other words, if you had known what you know now, you would not have approved it, is that correct?

Mr. GARDNER. That is correct.

Senator KENNEDY. Then why is it still on the market?

Mr. GARDNER. We are required to go through certain proceedings once a drug is approved before it can be removed from the market. We must issue an opportunity for a hearing, process the hearing request, and hold the hearing. While that takes place, the drug can continue to be sold. We cannot remove it at that point.

Senator KENNEDY. If I understand it, you had the only study which is basically discredited, and you would not approve it on a new drug with the information you have.

We had notice of this in April 1976. This is March 1977. The drug is still on the market, being used.

If that is the case—and I think I am stating it correctly—then how are we protecting the American people?

Should you not be up here asking us to change that or alter that?

Mr. MERRILL. Let me respond to that.

We urged Congress last year to enact legislation that would change the standard by which the agency could withdraw approval of both human and animal drugs based on a finding of concern about safety, in other words, to change the imminent hazard standard of the present law, which has been the only exception to the hearing first and withdrawal later procedures of the statute.

Senator KENNEDY. What is the agency doing now in terms of alerting the public, the elderly people, the doctors, those who use the drug?

Mr. GARDNER. At the time, the Bureau made its determination and took the first step, which was to issue a notice of an opportunity for a hearing. We made those findings public. They are available to physicians and patients who would then be able to understand the issue that had been raised and take appropriate actions in their own behalf.

Senator KENNEDY. What has been the effect of it? Has there been a reduction in the use of it or what? Are you monitoring that? Are you finding out?

Dr. CROUT. No; we are not monitoring it. It is a new drug introduced in the market. Its sales have grown because they begin at zero. There is no way to know whether an action of that type influences sales.

From the firm's point of view, it may not have grown as much as they would have liked. But our basic approach has to be the one of dealing with the safety and effectiveness issues and with the submission of applications. We do not use the press for the purpose of influencing sales at a time when we have administrative proceedings going on; to do so might undermine our own credibility in handling the administrative proceeding.

Senator KENNEDY. Do you not think there was something wrong if you would not have allowed it in the first place, and people are still using it?

Dr. Gross, is this a carcinogenic substance?

Dr. GROSS. No, sir.

Senator KENNEDY. You do not think it is?

Dr. GROSS. We have no evidence for that, sir.

Senator KENNEDY. Do you know that it is not?

Dr. GROSS. No; we do not know that it is not. There are some suggestions that it might be, but it certainly is not a definite carcinogen.

The matter is unresolved because of this poor study, I would say.

Senator KENNEDY. Nonetheless, you have a situation, as I understand it, where you would not have approved the drug in the first place with the information you have. You have got it out on the market now, and now you feel you cannot do very much in terms of informing the American people about the potential danger on this because it is going to interfere with the procedure which, at the minimum, has lasted 8 or 10 months.

When will this finally be resolved? What is your best estimate?

Dr. CROUT. May I point out that our case against the drug is not a safety case. Our allegation, and I put it in those terms because the Bureau is in a prosecutorial role, if you will, and the Commissioner's office is in a judgmental role at this point.

Our case is that untrue statements were submitted in the application, and that is all, and that they were submitted on a fact which was material. So in order to take the drug off the market, we must go through a lengthy administrative procedure that you are familiar with as a lawyer, and which we outlined here in subsequent testimony. This is what is taking time.

There is no doubt that once a drug is marketed, the burden shifts from the manufacturer to the Government in developing a case, and that is fundamentally why it is so much more difficult to carry on, to implement a decision after a drug is marketed.

Senator KENNEDY. Even when the information is faulty or inaccurate or misleading?

And what sense does that make?

Dr. CROUT. It does not make a lot of sense. That is the way the law is constructed.

Senator KENNEDY. It does not make any sense really. I mean you would not have approved it previously, and why would you not have approved it originally then?

Dr. CROUT. The study is essential in the Bureau's judgment. A study on the long-term toxicity is essential for the approval of any drug which is to be used long term in humans.

Senator KENNEDY. Is that not a safety issue?

Dr. CROUT. That is a safety issue.

Senator KENNEDY. So you do not need the safety issue standard here?

Dr. CROUT. Prior to approval——

Senator KENNEDY. I know the procedures that you save to demonstrate safety before and then the burden shifts—you just explained it—afterwards.

But you and I agree—I think any rational person would agree that does not make any sense. If you require a safety standard before approval, to say that afterwards there is not a safety standard which is necessary.

Dr. CROUT. I also want to point out one other feature of the law. That is, prior to approval, uncertainty on the safety issue results in no approval. After marketing, the burden shifts to the agency.

More uncertainty about safety is not one of the reasons for withdrawal.

Senator KENNEDY. Well, it seems to me that you are talking about new information, and where you have made a judgment in terms of the safety of the previous information, and the procedures which have been outlined here may make some sense—may make some sense—but I do not see how you could possibly draw the conclusion that it makes any sense at all when you are talking about faulty information, which was the basis for a decision to move ahead and approve the drug.

Dr. CROUT. I am not arguing sensibility. I am trying to explain the time frame.

Senator KENNEDY. We are obviously interested, because I think this reflects why it ought to be changed, and that we are going to attempt to do in our legislation.

Let us proceed.

Mr. GARDNER. As has been mentioned, the Bureau of Drugs published a notice of opportunity for hearing in the Federal Register of Friday, October 15, 1976, a proposal to withdraw approval of the new drug application for Naprosyn pursuant to section 505(e)(4) of the act.

Prior to publishing the Notice of Opportunity for Hearing, the Bureau had provided Syntex and IBT with an opportunity to show that the study was not so deficient as to make it unacceptable.

Syntex representatives met with the Bureau of Drugs on August 20, 1976, and presented three volumes of new data, including a reconstruction of the 22-month rat study. A Bureau of Drugs review of that reconstruction revealed that there was no basis for the Bureau to alter its conclusion, that the 22-month rat study was unacceptable.

On November 12, 1976, industrial bio-test was invited to attend an informal conference with the Bureau of Drugs to review the findings of our inspection of the firm. At that informal conference, chaired by Dr. Carl M. Leventhal, Deputy Director of the Bureau of Drugs, IBT responded with a written submission to the Agency, which was subsequently reviewed by the Bureau of Drugs. In the judgment of the Bureau staff, neither the conference nor the written response provided persuasive evidence that the 22-month rat study was acceptable.

Senator KENNEDY. When are the American people going to know whether this has got a clean bill of health or if there are some safety questions?

Mr. GARDNER. At the outcome of the proceeding.

Senator KENNEDY. Is it 6 months? Will they know by July 4? Labor Day? Christmas? Or next Easter?

Mr. GARDNER. It is likely to be a matter of months. I cannot predict with any certainty how many months.

Dr. CROUT. We believe, in the Bureau of Drugs, that the study needs to be repeated. It is already started. It will be late 1978 before those data are available. The issue is whether the drug will come off the market prior to that. We are attempting to do this. Meeting the current requirements of the law is a long, arduous way in order to do that. The absolute scientific answer to the study is another couple years away, in our opinion.

Senator KENNEDY. The study is completed in late 1978?

Dr. CROUT. There is a repeat study now going on.

Senator KENNEDY. Is it your policy to wait until the repeat study has been done?

Dr. CROUT. Absolutely not. That is why we are taking action to take it off the market.

Senator KENNEDY. It seems to me that we have got the cart before the horse on this. It is still on the market. There are still profits being made from this particular item. It would not have been on the market if, based on the study that was done, it was found to be faulty. It seems to me that what you are almost saying to some people is, well, if you can get that drug on the market, even with false or fallacious kinds of information, you can tie up the FDA for a long period of time and they are powerless to do very much about it. At least you are going to be able to tie them up on this, it would appear, for 18 months or 2 years.

We have got the incentives completely the wrong way when you are balancing financial incentives the wrong way and the protection of the consumer wrapped up the wrong way. I do not know if I see it correctly, but that is certainly the way I look at it.

Mr. MERRILL. I think that is absolutely right. I think that under current law, when the product is on the market the incentives are to utilize every legal avenue that the statute provides to keep it there, to prolong the process. That has been our experience.

Senator KENNEDY. Would your legislation have changed that?

Mr. MERRILL. The proposal would have changed the "imminent hazard" standard.

Senator KENNEDY. That is not the question. Would your legislation have changed this?

Mr. MERRILL. No, sir, it would not.

Senator KENNEDY. Ours will, and do you not think we should?

Mr. MERRILL. No question about it.

Senator KENNEDY. Will you help us try to get legislation that will?

Mr. MERRILL. We certainly will. We testified before Congressman Rogers last year in support of exactly that proposition, and we would support legislation here.

Senator KENNEDY. Well, at the present time it is a risk in terms of this product, and I would think, of other products. That is, I think the troublesome situation that you are faced with and the American people are faced with—you as the protector of the American people in this extremely important area.

Let's proceed.

Do you want to start on TCC, page 5?

Mr. GARDNER. Yes. Triclocarban is an antimicrobial agent used in virtually all antimicrobial-containing deodorant soaps now on the market. It is among the ingredients currently being evaluated in our extensive review of the safety and effectiveness of all over-the-counter (OTC) drugs.

TCC has been judged by the OTC antimicrobial panel handling this class of ingredients to require additional evidence of safety or effectiveness before the ingredient can be considered "generally recognized as safe and effective (GRAS and GRAE), as stated in their report published in the Federal Register of September 13, 1974.

The panel's judgment was that, before such general recognition could be granted, additional studies of TCC needed to be done to determine the blood levels of TCC which produce toxic effects in animals and to determine the blood levels produced in humans using TCC-containing soap so that the margin of safety was clearly documented.

Senator KENNEDY. Why was hexachloraphene taken off?

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Mr. GARDNER. It was removed from the market because it was absorbed through the skin and resulted in high blood levels which could produce toxic effects, brain lesions, and other effects that cause damage to the human system.

Senator KENNEDY. Absorbed through the blood stream?

Mr. GARDNER. Yes, sir. It was absorbed through the skin and entered the blood stream.

Senator KENNEDY. Is TCC absorbed into the blood stream too?

Mr. GARDNER. Yes; it produces a similar effect. It is the degree of absorption that is different.

Senator KENNEDY. It is what?

Mr. GARDNER. It is the degree of absorption that is different.

Senator KENNEDY. It is absorbed through the blood stream, is that correct?

Dr. CROUT. TCC is the least soluble. the least absorbed, of all the available agents that is antimicrobial effect in soap, which is why it has become so popular in that use since hexachloraphene was banned.

Senator KENNEDY. If I can get back to my question, is it absorbed?

Dr. CROUT. Yes; to some degree.

Senator KENNEDY. All right.

Mr. GARDNER. At the time the OTC Panel was reviewing TCC, the Panel used a long-term study in rats then being conducted by IBT for Monsanto Chemical, Inc., the manufacturer of TCC, to estimate that the margin of safety of TCC is 500- to 1,000-fold. In reaching its judgment, the Panel reviewed only 6-month and 1-year interim reports of the study, since the study was ongoing and other data were available at that time. A final report of the study was then submitted in 1976 and careful review of the raw data revealed a number of irregularities similar in type to those encountered in the Naprosyn study.

Monsanto and IBT attempted to resolve some of these problems in a meeting with representatives of the Bureau of Drugs, and in December 1976 a new version of the TCC study was submitted to FDA. This version is being reviewed and the position of the Bureau of Drugs in regard to TCC is being developed.

At this time, the staff recommendation is that the study should not be accepted, which means that TCC cannot yet be considered as "generally recognized as safe and effective."

Senator KENNEDY. What kind of problems were found?

Mr. GARDNER. Dr. Crout.

Dr. CROUT. With the study per se, Dr. Gross, can you comment on that?

Dr. GROSS. What were the problems with the TCC study?

Senator KENNEDY. Yes.

Dr. GROSS. The problems are very, very serious. In our scientific investigation staff, we have attempted to deal with these problems and we still do not have a complete picture. The main difficulty is that despite two meetings at least with Industrial Bio-Test, it is impossible to sort out what animals were on this study—how many animals were on the study, how many animals were kept in single cages or in group cages. There is utter confusion as to how the animals were numbered. They were placed from one part of the study to another one, and they died. It is impossible to conduct a thorough validation of indication of the animals. The records are completely inadequate. It is just a hopeless situation.

Senator KENNEDY. This is the basis on which approval is made, am I correct, Dr. Crout?

Dr. CROUT. No. This is not an example on which a basis of approval was made. TCC was approved in 1963, I believe, on the basis of toxicology studies at that time. This study was undertaken later by Monsanto, and its purpose now is to fulfill a new toxicological need identified by our OTC panel. So the absence of this study does not give us any new information supporting the safety of TCC, but neither does it reflect on the unsafety of TCC. In short, we know about as much about it now as we did in 1963.

Senator KENNEDY. Why do you bother? What is the significance of doing the study?

Dr. CROUT. The significance of doing the study is that our OTC panel—there are two motivations: Monsanto did the study on its own, and it apparently issued a press release today giving that account from its point of view.

From our point of view, a desire for the study is that in the course of the OTC review, we are now requiring a number of long-term studies which were not required when products were originally approved, and this looked like a study which would fulfill that purpose.

Senator KENNEDY. Why are you requiring it?

Dr. CROUT. Because most drugs approved prior to the late 1960's never had any long-term toxicology studies. In the course of re-reviewing those drugs, we are now seeking that information.

Senator KENNEDY. Why do you do it? Do you do it for fun or to harrass the company, or has it got a purpose?

Dr. CROUT. The purpose of this study is to identify the blood level in animals at which toxic effects occur.

Senator KENNEDY. Why is that important?

Dr. CROUT. You take that blood level and compare it to the blood level that is achieved in humans using the product and see what the difference is.

Senator KENNEDY. Does it have anything to do with determining the safety of the product? Is the study done for that purpose?

Dr. CROUT. It has to do with determining what we call a margin of safety.

Senator KENNEDY. All right.

Dr. CROUT. That is, if the blood level that it takes to produce the toxic effect in animals is many times higher than that which the product produces in humans, reasonable toxicologists can look at that and judge that that is safe for humans.

Our OTC panel, on the basis of the earlier information, felt the safety factor was 500- to 1,000-fold, which is an ample safety factor in our judgment.

Senator KENNEDY. The fact of the matter is, unless I do not understand English, is that it is basically done for a safety factor for some protection, am I not right in that?

Dr. CROUT. Along with the study in animals and the study in man are done together to determine safety——

Senator KENNEDY. You have got a safety study that is completely unjustified or unwarranted, deficient, is that correct?

Dr. CROUT. That is correct.

Senator KENNEDY. That is done by the same testing laboratory, IBT?

Dr. CROUT. That is correct.

Senator KENNEDY. You have got probably millions of Americans using this particular product.

Dr. CROUT. All those who wash, as far as we know.

Senator KENNEDY. Well, I think we got a good question and a good answer on that.

Let's move ahead.

Mr. GARDNER. A refusal to accept the IBT study would affect the marketing of products containing TCC, at least in the near term. Under the regulations governing the OTC review, marketed products can continue to contain ingredients which have not yet been determined to be generally recognized as safe and effective, providing they are not shown to be unsafe, for a specified period of time up to 2 years after the relevant monograph is final.

This period of time is provided so that research can be done to provide the essential scientific information needed for a final determination. If at the end of that time the essential data are not available, the ingredient then must be removed from OTC products being marketed under the monograph.

If new evidence of lack of safety appears at any time for a marketed drug, it is of course essential that we act promptly to minimize risk to the public health as we have done with hexachlorophene and zirconinium. This is not the case, however, for TCC.

The issue in regard to the IBT study of TCC in rats is not that it provides new evidence showing lack of safety; rather it fails to provide adequate information of a quality appropriate for the toxicological standards of 1977 to prove "general recognition of safety."

If the study is rejected, it will have to be repeated and the results will have to support safety before such general recognition can be granted.

Senator KENNEDY. Would you approve the product without the studies?

Dr. CROUT. We did approve it without the studies in 1963.

Senator KENNEDY. That is 1963?

Dr. CROUT. That is right.

Senator KENNEDY. In the new request would you have approved the product?

Dr. CROUT. The product is not up for approval. It is already on the market.

The answer is, if it were first coming on the market today, the answer is "No; we would not approve it without the study."

Mr. GARDNER. Because of the deficiencies in the particular studies described above, considerable effort has recently been made to determine whether other studies conducted by IBT may be flawed.

An informal working group chaired by Mr. Jerome Halperin, Deputy Associate Director for New Drug Evaluation, Scientific, has been meeting regularly since early this year to assess the scope of the problems identified and their impact on other studies or other products and to plan future study reviews.

We have only partial success in obtaining from IBT a list of all studies performed by that laboratory for products regulated by FDA. IBT has not been willing to provide the agency with a comprehensive list of all such studies, and we lack legal authority to compel this information.

Senator KENNEDY. Does this really make much sense? We have got two items here, and we are going to go into a number of others that you and I are familiar with, with similar kinds of problems and concerns by the staff with work done at IBT. This is a matter which came up before the committee almost a year ago.

Do I understand that you have not got the list of the drugs that IBT has done various studies on?

Mr. GARDNER. That is correct. We do not.

Senator KENNEDY. Have you requested it?

Mr. GARDNER. We have some studies.

Senator KENEDY. You do not have them all?

Mr. GARDNER. No.

Senator KENNEDY. Have you requested it?

Mr. GARDNER. Yes; we have.

Senator KENNEDY. What has been their attitude?

Mr. HALPERIN. IBT's answer has been that they feel that they can only divulge to the Government knowledge of those studies which have been submitted to the Government.

This is under advice of their counsel.

As a result, they have gone back to all—this is what they are telling us—the firms for which they have done studies, identified to those firms the study conducted, and have asked the firms to indicate which of these studies have been submitted to IND's or NDA's, and then IBT, through its counsel, sends us a list. That is on a sponsor by sponsor basis, and it is very slow.

Senator KENNEDY. Why would you not have come back at least to us on the committee here and asked us to subpena these matters?

Mr. HALPERIN. I do not think I am competent to answer that question.

Senator KENNEDY. What we are talking about, as I understand it, is a testing laboratory that does work for the EPA, do they not? For the Cancer Institute, do they not?

Mr. GARDNER. Yes.

Senator KENNEDY. The Bureau of Foods has got problems with them?

Mr. GARDNER. That is correct.

Senator KENNEDY. You have all of these that have been either demonstrated for drugs in the Bureau of Drugs, problems in the Bureau of Foods, there are two drug companies that have written in, as I understand it, saying they have problems in terms of reviewing the evidence, in terms of the conclusions with the findings of IBT.

What have we done? We have got all kinds of serious flaws in the scientific data and information provided. Where are we? We are 1 year down the road, and I do not see any really meaningful progress on it.

When we talked about this last year in terms of the scientific information of data, we had the Commissioner, Alexander Schmidt, and Frank Rauscher saying this was the most serious kind of potential health hazard that we are facing.

The EPA agreed with these various factors. Now we are 1 year down the road, and I do not see, in terms of this particular research laboratory that we have made any real progress on it.

We saw at the time we had some of the same similar problems with Searle, and we had Alexander Schmidt put a strike force in there, and we got some action.

You mentioned earlier about where some of that action has led to. It seems to me that this thing has been laid out even more compellingly, and I do not see what we are doing, or what you are asking us to do, or how you are going to deal with this in an effective way to protect the health and safety of the American people.

Mr. GARDNER. Well, we have tried to send people in there and obtain as much information as we could, using the authority that we have. We have obtained some information, although as you point out, it is not complete. We are going to take some steps within the next few weeks.

Senator KENNEDY. Next few weeks? Do you want us to subpena that material? We will issue that subpena. We will issue that subpena today, if you are asking that, and let us know what you want.

Mr. MERRILL. Can we provide an answer? We will do so by the end of the day. I think that a subpena could be very helpful. It is clear we are going to be asking for legislation to enable us to get this material routinely.

[The information referred to follows:]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

MAR 11 1977

Honorable Edward M. Kennedy
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

At yesterday's hearing on our bioresearch monitoring program before your subcommittee, you invited us to request the assistance of the subcommittee in obtaining access to a complete list of the studies performed by Industrial Bio-Test Laboratories on products approved or regulated by FDA and other Federal agencies. Specifically, you indicated a willingness to consider the issuance of a Congressional subpoena for that material. We promised to provide the subcommittee a response by the end of the day.

Our attempts to call you, Dr. Borowitz, or Mr. Fox yesterday evening were unsuccessful, but I was able to reach Mr. Fox this morning. As I have advised him, we believe that, as a result of your statements yesterday, a final attempt to obtain the information from IBT voluntarily may be successful. Last night the attached letter was sent as a telegram to Dr. Calandra, President of IBT, reiterating our insistence that the information be provided immediately or we would resort to the use of compulsory process.

We have in addition been in communication with the office of the United States Attorney in Chicago, which has expressed a willingness to consider the use of a grand jury's compulsory process to obtain the information if it is not provided voluntarily. If we do not receive a satisfactory response from IBT, we intend promptly to recommend a grand jury inquiry into the conduct and reporting of testing by that firm. One of the immediate purposes of such an inquiry would be to elicit, by subpoena, the information that is needed to facilitate our assessment of the continued approvability of products marketed on the basis of IBT-conducted tests. This approach would have the additional advantage of acquainting the United States Attorney's office with the findings and progress of our IBT investigation as it proceeds, which would shorten the time required to prepare and present any criminal enforcement action that might grow out of the investigation.

We will know within a matter of days whether one or the other of these approaches is likely to produce the information we need. We are hopeful that the disclosures at yesterday's hearing may provide the stimulus for IBT to provide the information voluntarily. However, if both approaches fail, or seem likely to leave the matter unresolved for any length of time, we will promptly return to the subcommittee and formally request whatever assistance, including the issuance of a subpoena, that you can provide.

Sincerely yours,

Shervin Gardner

Shervin Gardner
Acting Commissioner of Food and Drugs

Enclosure

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

March 11, 1977

Dr. Joseph C. Calandra
Industrial Bio-Test Laboratories
1810 Frontage Road
Northbrook, Illinois 60062

Dear Dr. Calandra:

On November 12, 1976, you and your associates and counsel attended an informal conference with staff of this Agency chaired by Dr. Carl M. Leventhal, Deputy Director of the Bureau of Drugs. The subject of the conference was the deficiencies found by the Bureau of Drugs in certain animal studies conducted by your laboratories. At that time, to assist FDA in expediting the identification and evaluation of all products whose regulatory status may be dependent upon studies conducted by IBT, Dr. Leventhal requested that you provide the Agency with a list of all studies conducted in your laboratories. Counsel for IBT, Mr. Merrill Thompson, acknowledged this request in his letter of November 19, 1976, to Ms. Anne Davidson of the General Counsel's office, and advised FDA of IBT's plan to provide these data.

The process identified by Mr. Thompson has proven to be unsatisfactory. Between January 11, 1977 and February 22, 1977, we have received 7 communications from Mr. Thompson providing us with the names of studies on drugs only which IBT has conducted for some 15 regulated firms. We still have no idea as to what fraction of the studies IBT actually has conducted those reported represent. We moreover, have no idea as to how many products including those under the regulatory jurisdiction of other FDA bureaus or other regulatory and scientific agencies may be affected.

As you may know, we testified on this date before the Senate Subcommittee on Health and Scientific Research of the Committee on Human Resources and the Subcommittee on Administrative Practices and Procedures of the Committee on Judiciary. Senator Edward M. Kennedy, Subcommittee Chairman, expressed his dismay at the slowness and inadequacy of your response and the consequent delay in our identification and evaluation of all studies conducted by your laboratories and their possible impact on the safety of products being consumed by the American public. We share his concern and impatience with your lack of full and responsive cooperation with our request of four months ago.

I would like to offer you final opportunity to comply voluntarily with our request that you provide a complete and accurate list of all studies conducted by your firm. We ask that you provide us within one week a

list which clearly identifies the sponsors, products, dates, and types (e.g. chronic, subacute, carcinogenicity, etc.) of all studies conducted by IBT since January 1, 1967. I would expect that you would also be prepared to provide, if requested later, a similar list of older studies conducted since the inception of your firm's activities.

I await a more responsive and forthcoming reply than we have received to date. I am prepared to utilize every legally available recourse to obtain this information as soon as possible in the absence of your voluntary cooperation. Please acknowledge receipt of this telegram within 24 hours indicating your intention to the above request.

If the information that I am requesting is voluntarily made available to FDA, the Agency will not disclose it to the public and will deny any request made under Freedom of Information Act on the ground that the information is confidential commercial information and part of an open investigatory file.

Sincerely yours,

Sherwin Garner

/s/Sherwin Garner
Acting Commissioner of Food and Drugs

Senator KENNEDY. This is something today—is it important, or is it not important? If it is important, we ought to move ahead on it. If it is not, then we have got a fundamental difference, obviously.

Mr. MERRILL. Very important. Very clearly the information is important. It is the one piece of information we are having difficulty getting from some other laboratories as well, even from those that are very cooperative.

It is clear it may well be useful to issue a subpena to get this information from IBT.

Senator KENNEDY. Have you examined what administrative remedies there exists within the Department, Secretary Califano's?

Mr. MERRILL. We have.

Senator KENNEDY. What is your conclusion?

Mr. MERRILL. Our judgment is that we do not have legal authority, nor does the present United States Code give us legal authority to demand the submission of that information.

Senator KENNEDY. Well, you let us know later today. I will do everything—it is obviously up to the members of the committee—but we will make every effort to submit that subpena.

Can you do a comprehensive job if you do not know the products involved?

Mr. GARDNER. We cannot. We obviously need to know what products are involved.

Having gotten that information, we will be required to go through the files in our Agency to see what the significance of that information is.

Therefore, there is a substantial effort that would be required.

Senator KENNEDY. Did you ever try and ask the drug companies themselves, those that were dealing with this laboratory, to submit to you the various drugs that they had used?

Mr. GARDNER. We do not know all the firms.

Senator KENNEDY. You do not know all the drug company firms? You know all the drug company firms that submit various products to you.

Mr. GARDNER. You mean just send a general letter to all of them?

Senator KENNEDY. Yes; a night letter. Ask them. I would be interested in the ones that responded, and also the ones that did not respond. And how many would we be talking about?

Mr. GARDNER. There are probably several hundred of the top drug companies that would be in that category.

Senator KENNEDY. Why do you not do that, just ask them?

Mr. GARDNER. We can do that.

Senator KENNEDY. The problem, as you have stated very well in your testimony, has to be considered a matter of enormous importance and significant consequence in terms of health.

You are not getting the information. I think you ought to exercise every bit of authority within your own—well, what you are doing, from a legal point of view, from the extra legal way of inviting the drug companies to respond on this particular question. And then we want to know later in the day whether you are making such a request of us in terms of subpenaing.

I think this is important, obviously, in terms of our whole legislative issue in question. If we can determine that from that particular information, that there is a range of different products, and that this

kind of authority ought to be available within the FDA when there is a serious kind of a situation as presented by IBT, and that you need that kind of legislative power in order to protect the American public, I think it is completely warranted and justified.

We want to hear from you later in the day if you think that that kind of information is essential to carry forward your general mandate in terms of the protection of the American people.

Do you want to finish the statement?

Mr. GARDNER. In summary, our investigations have shown clearly that in the view of the Bureau of Drugs, animal toxicology studies relating to Naprosyn and TCC are not scientifically acceptable. The Bureau has reviewed some studies on other drugs tested by IBT.

Our basic approach to handling problems at IBT will be to review important studies conducted there in the past on products under our jurisdiction.

We have designed a plan for completing our investigations of IBT-conducted studies, and are taking steps to carry out that plan.

That will summarize the discussion on Industrial Bio-Test Laboratories. May I ask if at this time I could briefly summarize the general program we have been conducting, and then perhaps go on to the other things?

Senator KENNEDY. I just have a few questions, and maybe we could wrap up the whole question, and then go on to the other matter.

I would like to direct your attention to just a couple of questions, Dr. Gross.

Can you tell us what Virazole is?

Dr. GROSS. Virazole is a molecular entity which is proposed for the prophylaxis and treatment of certain viral infections.

Senator KENNEDY. Is it not now on the market?

Dr. GROSS. No, sir. It still is in an investigational phase. My latest information, received this morning, is that there are currently no investigational studies being conducted in human subjects in this country.

Senator KENNEDY. Do you know what deficiencies were found with regard to that product?

Dr. GROSS. The first problem is that virtually all of the preclinical safety studies on Virazole were carried out by Industrial Bio-Test or IBT.

Senator KENNEDY. This is the same company we have been talking about?

Dr. GROSS. Yes, sir. There is only one other long-term study on Virazole that I know of, and that was conducted by Lederle. There are some questions about that also. Apparently, the animals were moved from one location to another; we do not know all pertinent aspects about that study yet.

Now the Virazole studies have not been inspected by us so far. The problems that we perceive today with the IBT studies, particularly the long-term study, the 2-year study, our perception of these problems is simply from reading this report, the report that was submitted to us. We have not inspected their records and compared them with ours.

Senator KENNEDY. Were there serious problems in the report?

Dr. GROSS. There are sufficiently serious problems that a detailed audit of such records is warranted; I can give you some examples of this. For example, there are references in the report which suggest that

the animals on this study come from a study with an entirely different agent. We have also had a preliminary report on this particular rat study, a long-term study, where they give 6 months, the mortality up to 6 months. In the final report the mortality up to 6 months is entirely different. It should have been the same.

Senator KENNEDY. So the tables show that——

Dr. GROSS. Inconsistencies.

Senator KENNEDY [continuing]. Different numbers of deaths, is that right, in the animals?

Dr. GROSS. That is correct, sir.

Senator KENNEDY. This report was made at the end of last year?

Dr. GROSS. When the report was submitted?

Senator KENNEDY. Yes.

Dr. GROSS. The Virazole long-term study was submitted, I believe, in August of last year; yes, sir.

Senator KENNEDY. When were the deficiencies found, do you know?

Dr. GROSS. The deficiencies were found toward the end of December. I have a memo addressed to me dated December 13.

Senator KENNEDY. Was their recommendation to do further studies, or to do an audit of the raw material?

Dr. GROSS. Yes. A recommendation was made by the Division of Anti-Infective Drug Products to inspect, in great detail, the records of this study.

Senator KENNEDY. Do you know whether it was done?

Dr. GROSS. It was begun last week.

Senator KENNEDY. When?

Dr. GROSS. It was last week that an inspector was sent to IBT to secure copies of the internal IBT records on the study. To date, there has been no detailed audit of these records made by the FDA.

Senator KENNEDY. What about Isoprinosine?

Dr. GROSS. Isoprinosine is another drug that has a sort of checkered career. It was submitted to two different divisions in FDA for review. The claims for this drug by the manufacturer are varied and they keep changing. Someone has said that this is a drug in search of a disease.

Senator KENNEDY. What kind of deficiency is found there?

Dr. GROSS. I can summarize this very quickly. A long-term animal study on Isoprinosine was carried out by Industrial Bio-Test and this is one study where we have inspected in detail the internal records of the firm against what they reported on this study. Although the Bureau of Drugs has not come to a final conclusion on this, my conclusion is that the report is replete with false information.

Senator KENNEDY. Did you say complete or replete?

Dr. GROSS. Replete. They understate the number of tumors that were found in this. There are numerous instances of false information throughout the report.

Senator KENNEDY. And this is IBT, is that correct?

Dr. GROSS. Yes, sir.

Senator KENNEDY. We have a note on a letter dated February 22 from Sandoz to the FDA which describes serious deficiencies. They are talking about an IBT study that was actually done for them.

I will make this a part of the record.

It says: "A high rate (22 percent, i.e., 10 percent of the entire study) of post-mortem autolysis among animals that died during the study

which precluded post-mortem examination of those animals. Mixups in data recording causing records to show that some animals died more than once"—that is an old story—"others disappeared and reappeared. Ambiguities in the final study report as to the number of animals actually examined post-mortem." And, fourth, "incomplete retention of original data."

I could have been reading that a year ago—we have got the same types of problems. This is about a company Sandoz raising those particular questions to the Food and Drug Administration. That is on another item, but the same company.

There are a number of items that have been raised covering a variety of different issues, all with similar kinds of problems in terms of deficiencies, lack of scientific data, information. We have to ask, since these are so similar to the problems last year, members of this committee, both Democrat and Republican alike, meeting with Dr. Schmidt, we thought we ought to do very significant monitoring of these kinds of issues and questions.

I would like to see if we could get into exactly what the FDA has been doing since we got the $16 million.

Dr. GROSS. I would like to correct my answer to an earlier question on the problem of the carcinogenicity of Naprosyn. You asked me whether I thought Naprosyn was a carcinogenic agent. My answer was that there were no clear indications of carcinogenicity for Naprosyn from the IBT study. I believe I did say there were some suggestions of that.

Senator KENNEDY. That is very important. Can you define that any more precisely?

Dr. GROSS. Yes, sir. We have received, as it was mentioned before by the Commissioner, a so-called reconstruction of the study by Syntex. Syntex, a firm from California, gave us their version of what the study really should have said. If one looks at this reconstruction and one makes a few additional, not unreasonable assumptions, it turns out that a borderline statistical significance emerges on the issue of tumorigenecity for Naprosyn. It is not at the 0.05 level, which is usually taken as significant, but it comes pretty close to 0.078 by my calculations.

There are some disturbing indications. One cannot say that it is an unequivocal carcinogen.

Senator KENNEDY. We just do not know on this. Still on the market. Dr. Crout?

Dr. CROUT. In view of Dr. Gross' last comment, I have to say that the position of the Bureau of Drugs is not to make an allegation of carcinogenicity for Naprosyn. I think Dr. Gross has made it clear that his opinion is not necessarily shared by everyone else. Our official position as a Bureau is not one of alleging lack of safety or positive evidence of carcinogenicity. The Bureau's official position is one of uncertainty on the issue of lack of adequate data.

Senator KENNEDY. Have they proved safety?

Dr. CROUT. They have not. That is clear.

Senator KENNEDY. Does the law require proving safety?

Dr. CROUT. Yes.

Senator KENNEDY. They have not proven it?

Dr. CROUT. Yes.

Senator KENNEDY. In terms of that, they are not complying with the law?

Dr. CROUT. They are complying with the law.

Senator KENNEDY. They are complying with the law that says if you are able to get it on, and even with false information, even though some people——

Dr. CROUT. No, they are complying with the law very fully. They are using it to the extreme, to prolong the proceedings. There is a long, drawn out procedure, as we have indicated.

Senator KENNEDY. I suppose that it is also the law, it means that the Bureau has some responsibilities and public obligation——

Dr. CROUT. As we pointed out repeatedly, we are trying to take it off the market. That is the purpose. I want to make clear that we are not alleging that this drug is carcinogenic. We are not prepared to defend that point of view, in spite of Dr. Gross' personal uncertainties on this.

Senator KENNEDY. Why are you trying to take it off the market? fact back in the application a year ago, in our judgment.

Senator KENNEDY. Does that raise a safety question?

Dr. CROUT. It does not say it is unsafe. It says the study was material to the safety judgment a year ago, and now there is uncertainty, in our judgment. There is absence of evidence, in our judgment, on long-term safety.

Senator KENNEDY. That is the reason you are taking it off?

Dr. CROUT. That is the reason the study is material. The legal reason we are taking it off is untrue statements of a material fact.

Senator KENNEDY. Why is that important?

Dr. CROUT. That is——

Senator KENNEDY. We don't want to spend all morning on it, Dr. Crout, but there is a safety issue which is involved, and no matter how you want to define it on that, the law requires that they be proven safe. They submitted information that is basically inaccurate, and you are having to comply with the statute, and following the procedures of the law in terms of removal.

There is a safety issue involved. That is all it seems to me. I cannot say it is unsafe. I am not a scientist. But it is an issue which is involved.

If I do not understand that, then correct me.

Dr. CROUT. It is a safety issue involved in the indirect sense.

I am trying to state our legal reasons for taking it off.

Senator KENNEDY. The legal reasons, we have heard the legal reasons.

Dr. CROUT. Later, after this hearing is over, we have to deal with public statements we have made about the reasons for taking a drug off the market.

I am trying to state that very carefully. We have had enough on this issue of lawyers complaining about public statements and what we are alleging, and what we are not, but I want to be very certain that we try to avoid another round of that with Syntex lawyers.

Senator KENNEDY. I do not think anyone who reviews your statements on it would be troubled at all about your position.

You feel that that is a very heavy weight, and a very heavy responsibility, as you said, for fulfilling your responsibilities, as you should. And we are looking at it, I suppose, from the point of view of the consumers who are wondering whether they ought to be taking this particular item or drug tomorrow, or tonight, and do not feel all the

compunctions you might feel in terms of the niceties of the legal situation on it.

If we could summarize your other statement, please.

Mr. GARDNER. When it became evident that we were going to be involved in a comprehensive bioresearch monitoring program, we started to plan to carry out that program and determined that the program ought to cover four major areas.

One program is the monitoring of preclinical laboratory testing facilities, which were maintained either by sponsors or by independent contractors to test drugs, biologics, food additives, and other chemicals.

A secondary concern is the monitoring of investigators and sponsors of clinical investigations.

The third area of concern is the monitoring of institutional review committees or boards.

The fourth area of concern is the monitoring of food additive research. This includes the inspections of laboratories which conduct studies in support of food additive petitions, as well as a food additive review program which would reevaluate the safety of food additives in accordance with current scientific criteria.

After the 1977 budget amendment was approved, which provided for over 600 positions, and more than $16 million, we created a steering committee to oversee the development of this program. The committee consists of the agency's top management staff, and is chaired by the Associate Commissioner for Compliance. All of the agency's bureaus rely to some degree on research data submitted by manufacturers, and are therefore involved in the monitoring activities. The steering committee provides the means to coordinate the interests and needs of different compliance programs.

Last November we published a proposal concerning good laboratory practice regulations. This proposal establishes requirements for a broad range of laboratory features, including the kinds and quality of personnel, facilities, recordkeeping, operating procedures, and the quality of studies bearing on approval or disapproval of drugs and other products. These regulations are an important part of our laboratory monitoring program.

With the publication of this proposed good labortory practice regulation, we began a pilot inspection program of about 40 laboratories. By the end of this month we will have completed the first stage of pilot tests, and will begin to evaluate the results. Forty-one firms were scheduled to be inspected under the pilot program.

As of the first of March, 29 of those inspections have been completed, and reports have been received on 12 of the 29. Seven firms are currently in the process of being inspected, and five more scheduled for inspection this month.

We have identified an additional 40 laboratories for inspection during the next quarter beginning in April. It is too early to reach firm conclusions, but the inspection reports we have received to date under the pilot program tend to demonstrate that the manner in which commercial safety testing has been conducted may not be as bleak as we feared earlier, notwithstanding the fact that there may be one or two laboratories that do have serious deficiencies.

As I mentioned, 12 inspection reports have been filed, and the conclusion regarding 9 of these inspections is that no regulatory action is indicated.

In the remaining three organizations some problems have been found which will require action by the laboratories to correct. These correction activities will be monitored by the Food and Drug Administration Inspectors.

As part of the bioresearch monitoring program, we will also be publishing a proposal to amend our present regulations for conducting clinical investigations. These amendments are in part editorial, and designed to make language consistent with the Department's regulations, and will also extend the institutional review committee concept to studies involving noninstitutionalized patients.

In addition, we have designed a program for inspection of 175 of the institutional review committees during this fiscal year. That program will be issued in April, after we have completed a training program for our inspectors.

Similarly, we have developed proposed regulations which will be used in monitoring clinical investigators and sponsors of new drugs. Compliance programs for the enforcement of these regulations are also being developed, and will be put into effect in the next few months. During this year, under this program our district officers will inspect 85 research sponsors, 165 clinical investigators, and 12 biolaboratories which conduct bioavailability work.

The fourth major component of the bioresearch program is food additive safety review. A plan for this review was completed and accepted, and the Bureau of Foods has begun the review process.

Regarding the important question of utilizing the resources for bioresearch program, we plan to allocate and hire all employees authorized for this program by the end of this fiscal year.

Approximately 350 experienced Food and Drug Administration inspectors have received advanced training to conduct drug investigator/sponsor and animal toxicology laboratory investigations. Approximately 320 scientists, investigators, and support personnel have been employed in this program.

Senator KENNEDY. Are you in your summary statement?

Mr. GARDNER. This is my summary statement for the program in general. That completes it.

Senator KENNEDY. Can we get a copy of it?

Mr. GARDNER. Yes.

[The prepared statement of Mr. Gardner follows:]

STATEMENT

BY

SHERWIN GARDNER

ACTING COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE THE

SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

COMMITTEE ON HUMAN RESOURCES

AND

SUBCOMMITTEE ON ADMINISTRATIVE
PRACTICE AND PROCEDURE

COMMITTEE ON THE JUDICIARY

UNITED STATES SENATE

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Mr. Chairman and Members of the Subcommittees:

We have been invited to appear here today to provide the Subcommittees with a status report on the Food and Drug Administration's (FDA) Bio-Research Monitoring Program.

As you know, this program began in July of 1976, following approval by Congress and the Administration of the necessary resources. Although funding for the program was not finally approved until last July, we began planning for it some months before in order to begin implementation as soon as possible. We are especially grateful to these Subcommittees and to you, Mr. Chairman, for your efforts in this area.

ORIGIN OF PROGRAM

During testimony before these Subcommittees on July 19, 1976, we discussed events which led to the establishment of the program and provided our first progress report on its implementation. We noted then that the program was established as the result of serious concern on the part of the Administration and Congress over findings of certain FDA inspections of research laboratories.

Under the laws which FDA administers, manufacturers are responsible for performing tests and submitting data to ensure the safety of drugs and other products which FDA must approve. The FDA requires that extensive animal and other types of human clinical testing be carried out in accordance with certain provisions of these laws.

For some time, the Agency has been concerned about the absence of industrywide standards for the conduct of bio-research studies. Until our inspection in 1975 and 1976, however, we had no reason to believe that the quality of research in some firms was disturbingly poor and that this circumstance might conceivably be common. We had proceeded on the assumption that the evidence submitted to support an application reflected high quality professional science. Based on this assumption, our practice had been to examine the results of scientific studies, as well as the adequacy of the procedures and methods described in written reports of those studies. With rare exceptions, where cause was demonstrated, we did not examine work in progress.

I should add that the deficiencies we uncovered in quality assurance were not confined to substances under FDA jurisdiction. As you know, we found there was a general problem shared by other agencies responsible for evaluating or regulating chemicals. This fact was confirmed by representatives from the Environmental Protection Agency (EPA) and the National Cancer Institute (NCI) at the hearing last July before these Subcommittees.

In the spring of last year, when it became evident that the needed additional resources might be approved, we began initial planning for a comprehensive bio-research monitoring program, which would embrace the full range of research areas relating to FDA. We also wanted a program which would be compatible with -- but would not unnecessarily

duplicate -- programs of other Federal agencies receiving similar types of research data. We determined that the program should cover the following major research areas:

1. Preclinical laboratory testing - These are approximately 450 to 500 toxicology laboratories maintained either by sponsors or by independent contractors, which test drugs, biologics, food additives and other chemicals on animals.

2. Investigators and sponsors of clinical investigations - There are several thousand investigators who conduct human drug and other trials for firms and other sponsors of testing. We will monitor both the investigator and the sponsor who usually work closely together in preparing reports on the results of test for submission to FDA or other agencies.

3. Institutional review committees or boards - These are the committees which review protocols, test procedures and results of human drug, device and biologic trials performed in institutional settings. The committees must be composed of persons with varying backgrounds, such as lawyers, clergymen and laymen, as well as scientists. They are appointed by the institution in which the study is done.

4. Food additive research - This activity will include both inspections or laboratories which have conducted studies in support of food additive petitions, as well as an

additive review program to reevaluate the safety of food additives in accordance with modern scientific criteria.

STATUS REPORT ON THE BIO-RESEARCH MONITORING PROGRAM

With the approval of the 1977 budget amendment, which provided 606 positions and $16.4 million for the first year of this program, former Commissioner Schmidt created a Steering Committee to oversee the development of a comprehensive Agency program. The Committee consists of the Agency's top management staff and is chaired by the Associate Commissioner for Compliance. In addition, task groups were established to develop a basic monitoring strategy for the four major areas of bio-research which I just mentioned. The authority and objectives of the Steering Committee and task groups were outlined in a June 11, 1976 memo from the Commissioner to the Policy Board members. I will submit a copy of that memo for the record.

All of FDA's bureaus rely to some degree on research data submitted by manufacturers and are thus involved in the monitoring activities. The Steering Committee provides the means to coordinate the interests and needs of different product compliance programs. Policy decisions and direction for monitoring the program are provided by the Steering Committee.

The task groups (i.e., Toxicological Laboratories; Institutional Review Committees; Clinical Investigators and Sponsors; and Food Additive Safety Review) were charged to:

1. Establish working inventories of firms and other entities to be covered by the program;

2. Draft regulations to serve as standards of performance;

3. Write and develop inspectional programs to enforce those standards; and

4. Develop manpower estimates for conducting program activities.

The products of these various efforts are reviewed and approved by the Steering Committee before being accepted. I reviewed and made final determinations of manpower allocations.

I would like now to bring the Subcommittees up to date on the progress of each task area in implementing this program.

Toxicological Laboratory Monitoring

On November 19, 1976, we published in the Federal Register proposed Good Laboratory Practice regulations (GLP's). This proposal addresses requirements for a broad range of laboratory features, including personnel, facilities, recordkeeping, operating procedures, and quality control of studies bearing on the approval or disapproval of drugs and other products. Recognizing the importance of these proposed regulations and the impact they may have on the safety testing community, we provided for 120 days

of comment and conducted a public hearing on these regulations during the public comment period on February 15 and 16 of this year. An estimated 400 to 500 people attended the hearings each day, and many thoughtful comments were presented which will be taken into account by the FDA in developing final regulations probably by this summer. As we anticipated, many of the comments centered on such issues as:

-- Should the GLP's be voluntary guidelines instead of mandatory regulations;

-- Would the benefits of the quality control units, required by the regulations, outweigh the costs;

-- Should the regulations apply across-the-board to university laboratories and nonprofit institutes as well as to commercial firms; and

-- Should the regulations apply to safety testing other than long-term toxicity studies.

The development of the GLP's is a complex and time-consuming essential first step. These regulations are the cornerstone for our laboratory monitoring program. With the publication of the proposed GLP's, we began a pilot inspection program of about 40 laboratories. The pilot program is designed to:

-- measure the practicability and applicability of the proposed GLP's;

-- test our inspectional strategy; and

-- provide us with some data on the state-of-the-art of toxicological testing when measured against the proposed GLP's and the types of problems discovered in our initial laboratory inspections.

By the end of this month, we will have completed the first phase of the "pilot" test and we will begin to evaluate the results. Forty-one firms were scheduled to be inspected under the pilot program. As of March 1, 29 inspections have been completed. Reports have been received on 12 of these 29. Seven firms are currently in the process of being inspected; five more are scheduled for inspection this month.

We intend to continue the pilot inspection program for a least another quarter to help determine the final form of our regulations and compliance programs. We have identified an additional 40 laboratories for inspection in the next quarter, beginning in April. Our evaluation of the effectiveness of the inspection program will not end with the "pilot" effort, but rather will be a continuous process. When this program is fully operational, we plan to inspect all toxicological laboratories sending us important data on regulated products at least once every two years.

While it is still too early to reach any firm conclusions, the inspection reports we have received to date under the pilot program tend to demonstrate that the manner in which commercial safety testing has been

conducted may not be as bleak as we feared earlier. As I just mentioned, 12 inspection reports have been filed. The conclusion regarding 9 of these inspections is that no regulatory action is indicated. In the three remaining organizations, some problems were found which will require voluntary action, monitored by FDA inspectors, to correct. In the event that these pilot inspections or future inspections uncover serious violations in an organization, we will, of course, take appropriate action to expand the scope of that investigation.

As you know, Mr. Chairman, we have encountered some serious problems in other investigations of animal testing laboratories which are not part of the pilot program. We are proceeding with these investigations. One such investigation about which the Subcommittee specifically requested information concerns Industrial Bio-Test Laboratories, Inc. I would like to submit a current status report on this investigation for the record.

One of the issues resolved in formulating the toxicological laboratory program was its applicability to foreign establishments. We have no clear authority to conduct inspections of foreign establishments; however, it is evident to us that we cannot impose stringent requirements upon domestic laboratories and at the same time, make no effort to apply the same standards to foreign laboratories conducting safety studies for American sponsors. We decided, therefore, to extend our laboratory inspection program to include foreign laboratories which conduct studies submitted to FDA in support of marketing applications. To this end, we have initiated discussions with foreign embassy officials

to apprise them of our intentions and to provide for an orderly process. We expect to receive the cooperation of most foreign governments and firms in this new endeavor. We are in the process of identifying several of the larger foreign laboratories for inspection during the next several months.

Institutional Review Committee Monitoring

In 1971, the FDA published a final order amending the investigational new drug regulations. The amendments provide that clinical investigations of new drugs on institutionalized human subjects be appropriately reviewed and supervised to assure adequate safeguards for the health, safety and welfare of subjects used in all phases of investigational testing. These regulations require the establishment of an Institutional Review Committee (IRC), or board, prior to the initiation of any clinical investigation on institutionalized subjects. In 1974, the Department of Health, Education, and Welfare (HEW) also published regulations requiring similar approval for studies funded under HEW grants or contracts which involved institutionalized patients.

As part of the Bio-Research Monitoring Program, we shall, within a few weeks, be publishing a new proposal which will amend our present regulations to include all of the improvements made in those of the Department and to extend the Institutional Review Committee concept to studies involving noninstitutionalized subjects.

In addition, we have designed a program for the inspection of some 175 of these IRC's this fiscal year. This program will be issued in early April, immediately after we have completed a training program for FDA District investigators.

I might also mention that we have requested the opportunity to present testimony before the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research at its forthcoming hearing on institutional review committees. That hearing is scheduled to take place on May 3, 1977, in Washington, D.C.

Clinical Investigator/Sponsor Monitoring

For several years we have conducted a program for inspecting the work of clinical investigators and their sponsors. It has been very limited however, due to insufficient resources and priorities of other activities. We are substantially expanding our previous efforts in this area as a result of the budget amendments. One part of this program will focus on the procedures used by sponsors to monitor clinical research; the other part will audit the data reported to the Agency in applications. Both approaches have been used in the past in the inspection of drug investigators.

We have developed two sets of proposed regulations which will be used in carrying out this expanded program. One proposal contains performance standards for monitoring clinical investigations by research sponsors and contract monitors; the other will revise current regulations dealing with the individual responsibilities of clinical investigators and the conduct of the study.

A compliance program for the enforcement of these regulations is being developed, and will be put into effect within the next few months. In 1977, under this program, FDA District offices will inspect 85 research sponsors, 165 clinical investigators and 12 bioavailability laboratories for compliance with the procedural requirements of the regulations. When the program is fully underway, we plan routinely to inspect major commercial sponsors at least once every two years.

Food Additive Safety Review

The fourth major component of the Bio-Research Program is the Food Additive Safety Review. A plan for this review was completed and accepted by the Commissioner, and the Bureau of Foods has begun the review process.

A major goal of this review is to update the safety profile of those ingredients which previously have been considered safe for use in foods, as well as substances which inadvertently enter the human food supply. We now know that it is not possible to rely indefinitely on the scientific judgment of a particular time, even if that judgment was based on the best data then available. Continued review of scientific regulatory decisions is essential because, over time, several factors come into play that can make the initial decisions obsolete. Changes in scientific knowledge and standards, along with changes in product use and consumption, can have a bearing on safety decisions regarding these products.

We plan to develop a current toxicological profile for each food and color additive, based on estimates of the amount of each of these additives consumers are exposed to in their daily diets. Toxicity profiles and exposure information will be updated periodically in order to assure that permitted food additives are not responsible for the induction of acute or chronic disease effects.

As part of the periodic evaluation, we will ask for additional safety information to be developed in certain cases so that as new lines of investigation are explored, the limited risks that approved uses present can be further reduced. This information will permit the best possible evaluation of the potential of each food ingredient to produce cancer, adverse effects on reproduction, effects on the fetus, heritable genetic damage, or other types of chronic disease.

The second major goal is to ensure the integrity and quality of the biological information submitted to the Agency in support of regulated food and color additives. We believe there are about 130 nonclinical laboratories, out of the total of 450 to 500 laboratories, which do toxicity testing on food and color additives. We have begun systematic inspection of these firms under the "pilot" effort mentioned earlier.

We have developed a comprehensive multi-year plan for conducting the food additive safety review. I would like to submit a copy of the five-year plan for the record.

We also established several task groups to identify the kinds of tests needed to be done, how these tests should be carried out and the priorities for the review. These include the following:

-- Toxicological Protocol Task Force - This group will establish protocols and quality factors for long and short-term feeding studies, reproduction and teratology studies, short-term screening and mutagenicity tests. It consists of representatives from the Bureau of Foods, the National Center for Toxicological Research, the National Cancer Institute, and the National Institute of Environmental Health Sciences; it met for the first time on February 25, 1977.

-- Criteria Setting Task Force - This group will establish criteria specifying the type of tests that must be conducted on individual food ingredients considering such factors as the level of human exposure to the additive and effects associated with substances of a similar chemical structure. It will be composed of representatives from the Office of the Associate Commissioner for Science, the Bureau of Foods, the National Center for Toxicological Research, the National Cancer Institute, and the National Institute of Environmental Health Sciences.

-- Priority Setting Task Force - To establish priorities for review, we will gather information from a variety of sources for comparison against a set of predetermined minimum safety standards. In setting priorities for review, flavors, spices, direct additives, and color additives will be considered as a group. This represents about 2,100 individual ingredients. Establishing priority list will begin the reevaluation process.

-- Toxicological Evaluation Committees - These committees will make an in-depth evaluation of each substance which meets the established standard in regard to available information on toxicity studies and exposure. As a result of this evaluation, a final safety decision will be made on each compound. They will consist of a senior toxicologist serving as chairman, a junior toxicologist, a pathologist, a chemist, and a scientific project administrator serving as executive secretary.

As part of these efforts, we have entered into several contracts with outside groups. In one instance, we have contracted with the National Academy of Sciences/National Research Council to conduct an industry use survey of direct food and color additives. These survey results, coupled with frequency of consumption data, will enable the calculation of the expected exposure consumers will have to individual additives.

Finally, with respect to indirect food additives, we plan to contract to establish "limit specifications" for basic resins and adjuvants used in containers. Once the specifications are established, containers will be fabricated and then analyzed to determine migration into specific foods.

Before concluding my discussion of the four major areas of our bio-research program, I should note that, as we conduct inspections in any of these areas, if we find instances of serious nonconformance with requirements, we will, of course, take appropriate regulatory action. There are several regulatory options that may be taken, depending on circumstances. They include:

-- rejection or termination of a study;

-- withdrawal of marketing approval;

-- disqualification of a sponsor, monitor or investigator; and

-- for falsification of submitted reports to the Agency, prosecution under Title 18 of the United States Code.

INTERAGENCY RELATIONS

Throughout the development of our Bio-Research Program, we have sought to obtain input from other Federal agencies. For example, prior to publishing the proposed Good Laboratory Practice regulations, we

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provided draft copies to a number of other agencies and Departments which we felt might have an interest. Their comments were used in preparing the proposal which was published last November. More recently, we have received from the National Institutes of Health comments on the draft of proposed regulations on institutional review committees which we hope to publish soon.

We have also established liaison contacts with a number of agencies, including the National Institutes of Health, National Cancer Institute, Environmental Protection Agency (EPA), Consumer Product Safety Commission, and the United States Department of Agriculture. These arrangements should facilitate coordination of efforts once our program has been implemented, and as we gain experience with the kinds of information which will be generated. We expect, for example, that compliance profile information on laboratories would be of interest and use to other regulatory agencies and to agencies which contract heavily for animal studies. In this connection, we have already begun to work with EPA in the conduct of joint inspections of four toxicological laboratories to determine how best our field investigators can perform the kind of data audit which EPA feels is necessary under its program and how long it takes to perform such audits.

Once these inspections have been completed, we will be in a position to meet with EPA officials and negotiate an equitable service agreement with that Agency.

We have also held several briefing sessions with personnel from the National Institutes of Health to explain the Bio-Research Monitoring Program to them and explore possible benefits of information exchange. The initial reactions we have received have been favorable. We plan to proceed with drafting memoranda of understanding to provide for mutual exchange of information and cooperation between our agencies.

POSITION ALLOCATION AND PROGRAM EVALUATION

Regarding the important question of utilization of the approved resources for the Bio-Research Monitoring Program, it is our intention that all positions will be allocated and employees hired by the end of 1977.

Approximately 350 experienced FDA inspectors have received advance training to conduct drug investigator/sponsor and animal toxicology laboratory investigations. Upon completion of the intensive, two-week course, including proper laboratory and data recording procedures, these inspectors became part of the investigational cadre available to conduct laboratory inspections. As newly hired personnel are trained to fill behind the Bio-Research Monitoring investigators, the program will continually expand, reaching the full implementation level in 1978. Thus far, approximately 320 scientists, investigators and support personnel have been employed for this program.

Educational Activities

To help assure that the Bio-Research Monitoring Program and its requirements are understood by industry and others engaged in this type of research, a cooperative educational effort by Government and private sector will be necessary. It is FDA policy to inform manufacturers and the public of the requirements of the Federal Food, Drug, and Cosmetic Act and regulations. We do this usually through briefings, speeches, media articles, publications, and workshops. The ultimate responsibility for training, however, rests with the regulated industry, although FDA may participate in such training activities in an advisory role.

We are now in the process of developing educational activities along these lines for the Bio-Research Monitoring Program. We have already begun to formulate plans to carry out our educational responsibilities concerning the laboratory inspection program and the GLP's once they have been finalized. We also are considering the publication of informational pamphlets and brochures dealing with clinical investigations and Institutional Review Committees. We contemplate making such material available to all clinical investigators and institutions involved in human research after regulations and compliance programs have been finalized.

Mr. Chairman, this concludes my prepared remarks. Bio-research monitoring clearly is an important program and will continue to receive our attention to assure that it is conducted effectively.

My colleagues and I will be pleased to respond to questions you or members of your Subcommittees may have.

Senator KENNEDY. You mentioned the pilot inspection program, about 40 laboratories.

When did that get started?

Mr. GARDNER. That was started last November.

Mr. Hile can respond more fully to the details about that program.

Senator KENNEDY. When did it get started?

Mr. HILE. Mr. Chairman, the program was issued to our field operations on the 1st of November.

Senator KENNEDY. I am sorry?

Mr. HILE. It issued to our field organization on the 1st of November.

Senator KENNEDY. When did it actually get——

Mr. HILE. The first inspection started around the end of December.

Senator KENNEDY. End of December?

Mr. HILE. Each of the inspections——

Senator KENNEDY. When did you get the money?

Was it July?

Mr. GARDNER. In July we received some authorization for funds and positions. At the beginning of this new fiscal year, beginning in October, we received the balance of the authorizations. We began hiring sometime during the summer.

Mr. HILE. You will remember, Mr. Chairman, that this was an interim quarter, as we moved from the fiscal year beginning in July to the fiscal year beginning in October, we were given advance authorizations for hiring, during the interim quarter, which we saturated and then implemented our full-hiring program after October 1.

Senator KENNEDY. There was not really any question you were going to get the money. You knew that after we had appropriated that in the course of the summertime, did you not?

Mr. HILE. Yes; it was just a matter of authorizations to hire.

Senator KENNEDY. Can you tell us what kind of inspections you have had, how many "for cause" and how many random inspections?

Mr. HILE. Yes.

The random or pilot program constituted 42 inspections planned. The "for cause" inspections, about eight, Mr. Chairman.

Mr. MERRILL. I think we may have to find that and submit it later in the day.

Senator KENNEDY. Can you tell us how many you have actually completed?

Mr. HILE. We had completed some 29 of those 42, at the end of February.

Senator KENNEDY. How many "for cause" have been completed?

Mr. HILE. With your permission, Mr. Chairman, I will find the exact number.

Those are handled separately, Mr. Chairman.

[The material referred to follows:]

BUREAU OF DRUGS INSPECTIONS

CIE/BIORESEARCH

CIE PROGRAMS (Obsolescent)	Fy 76	T.Q.	Oct-Feb.	Outstanding
Sponsors & Monitors (Cause)	6	1	3	0
Investigators (Cause)	8	1	3	0
Investigators (Random)	169	16	3	0
Preclinical Laboratories	4	1	2	0
Institutional Review Committees	21	14	7	3
Clinical Labs.-Bioavailability	0	0	1	0

BIORESEARCH MONITORING PROGRAMS			Remainder FY 77
Non-clinical Laboratories			
GLP's	4	16*	13
Data Audits			1
Sponsors (procedural)			27
Investigators			54
Bioavailability Laboratories			10
Clinical Investigator's (Data Audit)			106
Institutional Review Boards		100**	94

*6 in progress, 10 now being scheduled
**Sampled for "Pilot" Program

Senator KENNEDY. Dr. Gross, you have been involved very much, as we have heard over the period of the last few years, in terms of these various programs on monitoring and inspecting.

Are you involved in this program at all?

Dr. GROSS. Bio-research?

Senator KENNEDY. On the inspection programs, on the shaping up of the inspection program.

Dr. GROSS. No, sir, I have not been involved in that. I have participated in one certain section, but we were not involved in the task force that set up this system. The bio-research program is under the supervision of Mr. Hile, who chairs the overall Steering Committee. The Steering Committee oversees a number of task forces under this program. One of the task forces of interest to this preclinical investigation is the so-called toxicology task force.

We had representatives from the Bureau, as did every other Bureau in the Agency, but I was not a representative. I was not involved in it at all.

Senator KENNEDY. You were the primary figure, who was involved in the Searle and also in the IBT investigations, which have been among the most revealing investigations that have been shaped by the FDA. I am just trying to figure out why you have not been involved, or can you give us any evaluation of the inspection system that has been set up?

Dr. GROSS. I have seen the tabulation on the results of the inspections on which reports have been received so far. The final evaluation was that no action was indicated or only voluntary action was indicated. The question here is, it is very difficult to compare surveillance inspection to "for cause" inspections. I can think of an analogy that would make this clear.

Suppose we are concerned that there is an occupational hazard of some sort. Suppose that the miners that mine for a certain commodity are believed to be at risk for some sort of disease, and we had concern over that. It would be proper to then focus one's attention to the population at risk, the miners in this case, that are involved in this occupation rather than take a random sample of the entire population, and see what is prevalence of whatever this is.

It is the old story, a random sample may not be sufficiently focused on the issue.

There is another feature here—these inspections were done with essentially new people, headquarter scientists, many of them who have had no experience in this kind of work, and the inspectors had received its 2-week course for the most part, but the fact that these inspections turned up essentially——

Senator KENNEDY. How much investigation can you learn in 2 weeks?

Dr. GROSS. Not very much, sir.

What I am trying to say is that even one company, for instance we were talking about Industrial Bio-Test, it is not a question of how many companies are all right and how many are questionable and how many are substandard, it is the sheer weight of the work that counts.

One large contract, a laboratory like that, is responsible for one heck of a lot of study submitted to the Food and Drug Administration, whereas individual manufacturers may not submit very much.

That is the problem.

Senator KENNEDY. Mr. Hile.

Mr. HILE. I wanted to expand on the comment about 2 weeks of training. That comment leads into the kind of program that we developed and are implementing. The 2 weeks of training was given to our most advanced drug inspectors who had already received a number of weeks of specialized drug training through their careers. They are all at advanced grade levels in our field investigation staff. Therefore, it was not a matter of our bringing new hires into the organization, giving them a 2-week training course in how to inspect laboratories and then turning them loose to make inspections of laboratories. Instead, we are hiring people at the entry level and bringing them in and training them to do the kind of inspection work, not nearly as sophisticated work, that they can quickly learn, and thereby relieve others to do the more complicated work.

It has a domino effect. Our inspectors that are participating in this program are our senior drug inspectors.

Senator KENNEDY. Dr. Crout.

Dr. CROUT. I would like to comment on the strategy of how this area is handled and draw a distinction between the GLP program and the "for cause" program, because it is not an issue of anybody being left out. Everybody is working terribly hard in overtime in order to get both accomplished.

One of our programs is to set up regulations for the performance of laboratories and see that they are enforced. That is the GLP program. It is run by an agency task force. We, purposely, in the Bureau of Drugs did not put any of our experienced case-handling people on that task force. I did not want them diverted from their case handling into simply administrative planning and administrative procedure.

None of the people who were on the Searle task force were part of that task force. We had to educate new people for that job. We have observed our case-handling people, like Dr. Gross, for the "for cause" program which was going on simultaneously, and also used the case-handling people in a faculty role in the training course for other investigators.

So I think it is not a matter of anybody left out. It is a matter of everybody working overtime at best advantage to get both parts of this program going.

Senator KENNEDY. How did you decide that you are going to do x number of random and x number "for cause"?

Mr. HILE. Mr. Chairman, the pilot program did not include the "for cause" inspections. Seven firms were inspected over the last year "for cause." Those are identified as a result of our scientists' review of data currently before the Agency.

We have some reason to believe that there is a problem, when these inspections are undertaken.

Senator KENNEDY. Is that all the ones that they recommend, just those seven?

Mr. HILE. Yes, sir, that is correct.

Senator KENNEDY. None of them recommended any others?

Mr. HILE. I guess I do not understand your term "recommended," Mr. Chairman.

Senator KENNEDY. The question is as to how many "for cause" recommendations were issued by the Department, just these seven, is that correct?

Mr. HILE. Yes.

These seven firms were identified during the course of review requiring "for cause" inspection.

Mr. MERRILL. I think, Mr. Chairman, your question is, were there other firms identified or recommended for "for cause" inspections, which did not take place.

Maybe Dr. Crout has the answer to that.

Dr. CROUT. Yes.

We have tips and we have some places we would like to go, but I do not want to name names. The case handling business is hard, as you have seen.

When you have two or three big cases going, it takes up the full staff. I suspect there will be some "for cause" inspections in the future.

Senator KENNEDY. I hope so.

Dr. CROUT. In addition to some of the firms mentioned, and there are some waiting their turn literally, so case-handling people have time to handle it.

Mr. GARDNER. Senator Kennedy, if I might, we tried to distribute the people we were getting assigned to these programs to do two things at the same time.

The first thing was to find out rather quickly the extent to which the problems that were identified during the past year existed generally throughout the laboratories that were testing the products.

The second thing was to allocate some resources to follow up those "for cause" instances which came to our attention by one way or another.

By this summer, we should have a better feel for the extent to which this exists, and we will be able to reallocate resources to more effectively take into account those "for cause" needs and those general monitoring needs which our pilot program indicates is appropriate.

Senator KENNEDY. I think, quite frankly, that it makes a good deal more sense to try to follow up on tips and recommendations of ideas of people that are further on down the line that are dealing with raw data and raw information, quite frankly, than sort of covering the waterfront.

Obviously, there has to be some balance. But it appears to me that the wiser targeting of the resources which are available and the professional power that you have would be more wisely spent in looking in these particular areas.

Obviously you are going to have to do some random, but it would appear to me that this is the area. The fact of the matter is we get tips. We look into it, and we find the problem.

We end up blowing the whistle on the type of thing on it.

It seems to me that, hopefully, you would be beating us to the punch every time on a lot of these questions and issues, and moving into those particular areas with review and using the full resources that you have, I think, makes a good deal more sense. That is the point I would like to make.

I have one chart here about various inspections. These are just on clinical inspections. This was an aspect of both justification for authorization and an area which we found in the earlier periods warranted additional kinds of review.

Do you have this chart? It is a Bureau of Drug Inspections CIE/ Bureau of Research. CIE programs. Are you familiar with this chart here?

Mr. GARDNER. Yes; I have a copy of that chart.

Senator KENNEDY. We see in the CIE program, fiscal year 1976, then the transitional quarter, and then October–February, which is the other quarter. It would appear just adding the transitional quarter and the October–February quarter, that is half the year, that not as much is being done this time as was done prior to the time of our whole investigation.

Then if you get the remainder—well, there is sort of a flurry of activity—I do not know whether that is as a result of the holding of these hearings or whatever, but it just seems to me that in that half-year period you are not even issuing up in terms of 1976—not that statistics tell the full story, but I would like to get at least some kind of explanation for this.

Dr. CROUT. The observation is correct.

Senator KENNEDY. Which observation?

Dr. CROUT. The numbers are correct. There have been fewer inspections of clinical investigators of the random type and some others at the present time. That is because Dr. Kelsy and Dr. Gross, Mr. Halperin and so on, their staffs, who are responsible for this, have had to take time out for revising of compliance programs, development of new regulations, doing all administrative work that is required to build the new program and so on.

The case-handling business has slowed temporarily while we build that administrative foundation for the new program that is not ideal, but I think it is an inevitable consequence.

Senator KENNEDY. That is going to be a tough thing——

Dr. CROUT. Inevitable consequence of new program getting off the ground.

Senator KENNEDY. It is amazing that we find a problem that demands your subsequent action on it, then we go out and get additional kinds of resources for it, and we all make the case for it, and then, as a result of the new emphasis on this, we see basically a slowing down and reduction of emphasis.

Dr. CROUT. For a period of time while the whole thing is built.

Senator KENNEDY. A 6-month period in any event on that, and a reduction.

I would think we would have a tough time in terms of the Appropritaions Committee in trying to get resources to you to do this, to come on back and say that this is what is justified and warranted.

As a matter of fact, the recommendations that you made were cut by the Appropriations Committee, and still it is really a dramatic reduction.

If you want to submit an explanation for the record, you could give us a projection as to where you are going in the next 6 months and what you see as a flow chart on that.

Dr. CROUT. Yes.

[Information subsequently supplied for the record follows:]

Human Drugs: Bio-Research Monitoring

Bureau Priorities	
R	1
PI	1
ECP	13

POSITION DISTRIBUTION

	Total FY 76 Pos.	Total FY 77 Pos.	Total FY 78 Pos.	Increase over previous Position Level FY 79L	FY 79H	FY 79D
Bureau	26	82	82	0	0	0
Field	28	147	147	0	0	0
Research at NCTR	0	0	0	0	0	0
CAO	0	0	0	0	0	0

DOLLAR DISTRIBUTION ($000)

	Total FY 76 Dollars	Total FY 77 Dollars	Total FY 78 Dollars	Increase over previous Resource Level FY 79L	FY 79H	FY 79D
Project Contracts	0	0	0	0	0	0
State Contracts	0	0	0	0	0	0
Grants	0	0	0	0	0	0
Research at NCTR	0	0	0	0	0	0

FY 77

Standards (2%)

Publish proposal on regulations for monitoring clinical investigations by sponsors.

Publish proposal on revised regulations for the conduct of clinical investigations.

Surveillance/Compliance (94%)

Initiate a compliance program for conducting inspections to determine sponsor adherence to the monitoring regulations, and the adequacy of facilities and procedures utilized by Bioavailability laboratories.

Initiate a compliance program for conducting inspections to audit the data of selected clinical studies by clinical investigators, including bioavailability studies.

Conduct inspections and complete review of inspection reports in the following target groups:

Sponsors	27
(assoc. clin. invest.)	54
Bioavailability Labs.	10
Clinical Investigators (including Bioavailability)	106
Non-Clinical Labs	
GLP's	33
Data Audits	1
Institutional Review Boards	94

FY 78

Standards (2%)

Publish final regulations.

Publish final regulations.

Surveillance/Compliance (94%)

Evaluate compliance program effectiveness and revise as necessary.

Evaluate compliance program effectiveness and revise as necessary.

Conduct inspections and reviews in the following target groups (anticipated level of activity):

Sponsors	107
(assoc. clin. invest.)	214
Bioavailability Labs.	40
Clinical Investigators (including Bioavailability)	425
Non-Clinical Labs.	
GLP's	51
Data Audits	4
Institutional Review Boards	375

FY 79 Low

Standards (2%)

Review and revise as needed after compliance implementation.

Review and revise as needed after compliance implementation.

Revise other regulations in this project area as needed.

Surveillance/Compliance (94%)

Same as FY 78

Same as FY 78

Same as FY 78

FY 79 High
(Increase Over Previous Level)

FY 79 Desired
(Increase Over Previous Level)

MEMORANDUM OF MEETING

July 6, 1976

Present: Frances O. Kelsey, M.D., HFD-108
Adrian Gross, DVM, HFD-108
William D'Agunano, Ph.D., HFD-102
David Richman, Ph.D., HFD-150
Mr. Manfred Hein, HFD-150
Mr. Jerome A. Halperin, HFD-101

and

Marion J. Finkel, M.D., HFD-100

Subject: 1. Inspection of Industrial Bio-Test, Inc.
2. Naprosyn (naproxen) NDA 17-581.

The meeting was called to discuss Dr. Kelsey's memo of July 2, 1976 (attached).

Dr. Gross and Mr. Hein detailed some of the inadequacies of the 22 month rat study performed with naproxen by IBT. It appears as though the study is so deficient that one cannot place any confidence in it. To our knowledge, there is no other long-term animal study with naproxen. However, Dr. Richman will phone Syntex this week and inquire whether there are any additional recently completed studies, perhaps done in the U.K. or Japan.

There was a discussion on whether naproxen should be removed from the market pending completion of new long-term studies, if no others are currently available. In view of the fact that there are three other recently approved non-steroidal anti-inflammatory agents on the market, all with about the same spectrum of therapeutic effect as naproxen, there was general agreement that we would recommend to the Bureau Director that naproxen be withdrawn. Whereas it is true that many old drugs on the market have not undergone adequate long-term animal studies, either, they at least have been used for prolonged periods in humans so that long-term safety data are available. Since naproxen does not meet our current standards and since its withdrawal would by no means create a therapeutic hardship, the choice of action seems clear. There was some talk about labeling the drug to indicate that adequate long-term studies have not been done but this action would seem to be appropriate only if naproxen were a unique drug.

It was agreed that we needed to do an expedited audit of the chronic animal studies of ibuprofen, tolmetin and fenoprofen, although our action on naproxen should not await those audits.

Dr. Gross and Mr. Hein will complete their report on the IBT naproxen audit this week. Dr. Richman will then prepare the memo to go to HFD-1 and HFD-2 on our recommendations (assuming that there are no other long-term studies).

With respect to IBT, itself, the firm will be asked to come in for a meeting.

Marion J. Finkel, M.D.

Attachment

cc:
Orig. NDA 17-581
HFD-1/Dr. Crout
HFD-2/Dr. Leventhal
HFD-108/Drs. Kelsey and Gross
HFD-150/Dr. Cyrfas
HFD-150/Dr. Richman/Mr. Hein
HFD-101/Mr. Halperin
HFD-102/Dr. D'Agamnno
MJFinkel:cks 7/7/76/7/23/76

OPTIONAL FORM NO. 10
JULY 1973 EDITION
GSA FPMR (41 CFR) 101-11.6

UNITED STATES GOVERNMENT

Memorandum

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

TO : DENNIS B. MIRACKY
Supervisory Investigator

DATE: July 15, 1976

FROM : CATHERINE KING
Investigator

Syntex Corporation
(Syntex Research)
Palo Alto, CA

SUBJECT: Naproxen (IND 5281, NDA 17-581)
Chronic Toxicity/Carcinogenesis Study Done
by Industrial Bio-Test Laboratories, Inc.
Northbrook, Illinois 1969 - 1971

HFD-108 (J.W. Holten, Dr. A. M. Gross)/SAN-DO (F.W. Scholl, Acting DIB) 7/14/76 telecon and TWX requested an investigation at Syntex to discuss with Dr. Robert Hill a letter and any other records related to Syntex' contacts with IBT about the above study.

CHI-DO's 6/21-24/76 inspection of IBT found serious deficiencies in the study. The results of the study were submitted to FDA by Syntex in support of the IND for Naproxen, an anti-inflammatory drug used in the treatment of arthritis. The NDA was approved in March 1976.

Dr. Adrian M. Gross, Pathologist, Scientific Investigations Staff (HFD-108), accompanied me on this investigation. On 7/15/76 we showed our credentials to Tony A. Bourdakis, Associate Director of Regulatory Affairs for Syntex Corporation, and Robert Hill, Ph.D., Assistant Director, Institute of Clinical Medicine (one of the divisions of Syntex Research). We issued the Notice of Inspection (FD-482) to Mr. Bourdakis. Both Dr. Hill and Mr. Bourdakis took part in the discussion. Dr. Hill gave us the copies of the protocol and letters attached as Exhibits 1 - 3.

Dr. Hill stated that Syntex entered into a contract with IBT in 1969 in which IBT agreed to do long-term rat toxicity studies following the attached protocol, Chronic Oral Toxicity Study In Rats With RS 3540, (Exhibit 1).

July 16, 1976

→ TO: HFD-108
ATTN: John Holten

Investigation and collection of pertinent documents involving Naproxen (IND 5281, NDA 17-581) completed July 15, 1976. Information attached as requested.

Dennis B. Miracky
DENNIS B. MIRACKY
Supervisory Investigator

We asked Dr. Hill what steps Syntex took to assure themselves that IBT was able to do the work. Dr. Hill said he visited the laboratory in 1969, before the study began. He spoke with Dr. Joseph Calandra, President of IBT and also interviewed Dr. M.L. Keplinger, Manager of the Toxicology Department at IBT. Dr. Hill said his visit was mainly to satisfy himself that the laboratory had adequate facilities and equipment to do the work required of them.

After the study began, Dr. Hill said, Syntex' Director of Toxicology, Dr. Bela Szakacs, visited IBT. This visit was sometime in 1970. Dr. Szakacs told Dr. Hill he thought the animals could be handled in a better manner, cleaner cages for instance, but he had no serious criticism of the animal facilities. Dr. Hill said their opinion was that Syntex might have done it differently, but IBT's procedures were considered acceptable by 1969 - 1970 standards. Neither Dr. Hill nor Dr. Szakacs examined any raw data or the methods used to obtain it by IBT.

We asked Dr. Hill if either he or Dr. Szakacs made any report or record of their visits to IBT. Dr. Hill said there was no written record of their visits.

The protocol (Exhibit 1) required reports quarterly and at the end of the study. Dr. Hill said they received reports from IBT at the stated intervals, but sometimes "under duress," meaning that Dr. Hill had to contact IBT and ask them to send the reports.

Dr. Hill said the final report was submitted to Syntex by IBT on or about November 1971. After he reviewed the report, he found a large number of errors, discrepancies and omissions of data. Dr. Hill said he consulted his supervisor, Dr. Kenneth Dumas, Senior Vice President of Syntex Research and Director of the Institute of Clinical Medicine. Dr. Dumas told Dr. Hill the toxicity study was his responsibility, and if IBT could correct the omissions and errors in the report to Dr. Hill's satisfaction, then Dr. Dumas had no objection.

Dr. Hill wrote Dr. Calandra on 11/18/71, expressing his dissatisfaction with the report. He said he had indicated the errors and omissions in red throughout the report and stated, "From past experience I am convinced that the report would be rejected by regulatory agencies in the U.S., U.K., Canada and Germany." (Exhibit 2).

We asked Dr. Hill if he had a copy of the first report submitted by IBT to Syntex. Dr. Hill said he did not, that the original report, annotated by him, was returned to IBT in November 1971. Dr. Hill explained that he did not keep a copy of the original report because he felt there was a chance it might be confused with the second, acceptable report.

We asked Dr. Hill what specific information was unsatisfactory or in error in the original report. Dr. Hill replied that the most significant omission was the complete lack of data on the histology of animals that died during the course of the study. This was required by the protocol, page 3, paragraph E. 1. (Exhibit 1).

Dr. Hill said there was no further contact between him and IBT until 3/3/72, when Dr. Hill received the revised report of the study, with the 3/2/72 cover letter from Dr. Keplinger (Exhibit 3).

After he reviewed the second report, Dr. Hill said he felt that it contained the needed information. He said he thought the study might be open to criticism, but there was enough data to make a valid conclusion. Also, the kind of toxic response shown in the IBT report was consistent with long term studies done for other drugs. We asked Dr. Hill if any additional laboratory work was done by IBT in preparing the second report. Dr. Hill said he thought not, that the report was simply rewritten to correct the errors and include the information specifically requested by Syntex.

We asked Dr. Hill if he made any contact with FDA to express his doubts about the study's validity. Dr. Hill replied that he had, but he was very reluctant to talk about it, since it could not be discussed without impugning people in FDA. We said we thought it was important that we have all information about any contacts between Syntex and FDA in this matter. Mr. Bourdakis said he would contact their legal counsel and ask if this could be discussed with us. Mr. Bourdakis left the room to make the phone call, and when he returned a few minutes later said they would tell us about it. After again expressing his reluctance to involve an FDA employee in any difficulty, Dr. Hill said he had talked with Victor Berliner in the Bureau of Drugs some time after November 1971 and before March 1972. Dr. Hill said he told Dr. Berliner about the original unsatisfactory report, that IBT was preparing a second report, and asked Dr. Berliner's opinion of what they should do. Dr. Hill said he remembered Dr. Berliner's response clearly. Dr. Berliner told Dr. Hill to send the report to FDA, and let FDA be the judge of it. The final, corrected report was submitted to FDA by Syntex in March 1972.

We asked Dr. Hill if there was any record of this conversation between him and Dr. Berliner. Dr. Hill replied there was no memorandum or other written record of the conversation.

We asked Dr. Hill about other studies done in support of the Naproxen IND. Dr. Hill said one month and one year studies were done with miniature pigs at IBT laboratories in Wisconsin. Syntex did none of the toxicity studies, since they did not have complete laboratory facilities at that time. Dr. Hill said the rat toxicity study done by IBT was the only long-term toxicity study done in support of the Naproxen IND.

The only other study ever done by IBT for Syntex was a one month study for vaginal irritation in beagle dogs using Vagitrol cream.

The Naproxen protocol also required IBT to submit tissue blocks and slides to Syntex. Syntex' pathologist was to spot check the slides and report any gross deviations from IBT's findings to Dr. Hill. Dr. Hill said there were no apparent discrepancies. Syntex is now re-examining all of the tissue slides submitted to them by IBT. Dr. Hill checked with his secretary on the progress of the examination, and she reported that the slides covering the low-dose and mid-dose animals have been completed. Dr. Hill said that he would send a copy of the report to Dr. Gross when the examination was finished.

We asked Dr. Hill about any contacts between Syntex and Dr. Horowitz, identified by Dr. Gross as chief medical adviser to Senator Kennedy. Mr. Bourdakis said Dr. Horowitz had called Mr. Hans Wolf, a vice president of Syntex Corp., on 7/13/76. As a result of their telephone conversation, Mr. Bourdakis said copies of the chronic oral toxicity study protocol, the 11/18/71 letter by Dr. Hill and the 3/2/72 letter from Dr. Keplinger (Exhibits 1, 2, 3) were delivered to Dr. Horowitz by messenger on 7/13/76.

Both Dr. Hill and Mr. Bourdakis expressed their desire to cooperate with FDA and supply all information requested of them. They asked about the results of the inspection at IBT. Dr. Gross explained that the final report had not been submitted, and he was not able to discuss the inspection at this time. Our interview with Dr. Hill and Mr. Bourdakis ended at approximately 12:15PM.

Catherine King
CATHERINE KING, #235

Attachments: 7/14/76 Assignment memo and TWX
FD-482
Exhibits 1 - 3 (6 pages)

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

1. DISTRICT ADDRESS
DHEW/FDA
50 Fulton St. Rm. 528
San Francisco, CA 94102

2. NAME AND TITLE OF INDIVIDUAL
Tony A. Bourdakis, Assoc. Dir of Reg. Affairs

3. DATE
7/15/76

4. FIRM NAME
TO Syntex Corporation

5. HOUR
9:50 a.m.
p.m.

6. NUMBER AND STREET
3401 Hillview

7. CITY AND STATE
Palo Alto CA

8. ZIP CODE
94304

Notice of Inspection is hereby given pursuant to Section 704(a) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374 (a)][1] and/or Part F or G, Title III of the Public Health Service Act [42 USC 262-264].[2]

9. SIGNATURE *(Food and Drug Administration Employee(s))*
Catherine Li / [signature]

10. TITLE *(Food and Drug Administration Employee(s))*
Investigator / Sis. Toxicologist

[1] Applicable portions of Section 704 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 374] are quoted below:

Sec. 704. (a) For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (1) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein. In the case of any factory, warehouse, establishment, or consulting laboratory in which prescription drugs are manufactured, processed, packed, or held, inspection shall extend to all things therein *(including records, files, papers, processes, controls, and facilities)* bearing on whether prescription drugs which are adulterated or misbranded within the meaning of this Act, or which may not be manufactured, introduced into interstate commerce, or sold, or offered for sale by reason of any provision of this Act, have been or are being manufactured, processed, packed, transported, or held in any such place, or otherwise bearing on violation of this Act. No inspection authorized for prescription drugs by the preceding sentence shall extend to (A) financial data, (B) sales data other than shipment data, (C) pricing data, (D) personnel data *(other than data as to qualifications of technical and professional personnel performing functions subject to this Act)*, and (E) research data *(other than data, relating to new drugs and antibiotic drugs, subject to reporting and inspection under regulations lawfully issued pursuant to section 505 (i) or (j) or section 507 (d) or (g) of this Act, and data, relating to other drugs, which in the case of a new drug would be subject to reporting or inspection under lawful regulations issued pursuant to section 505 (j) of this Act)*. A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

[2] Applicable sections of Parts F and G of Title III Public Health Service Act [42 USC 262 – 264] are quoted below:

Part F - Licensing – Biological Products and Clinical Laboratories and******

Sec. 351(c) "Any officer, agent, or employee of the Department of Health, Education, and Welfare, authorized by the Secretary for the purpose, may during all reasonable hours enter and inspect any establishment for the propagation or manufacture and preparation of any virus, serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or other product aforesaid for sale, barter, or exchange in the District of Columbia, or to be sent, carried, or brought from any State or possession into any other State or possession or into any foreign country, or from any foreign country into any State or possession."

Part F – ***** Control of Radiation.

Sec. 360 A(a) "If the Secretary finds for good cause that the methods, tests, or programs related to electronic product radiation safety in a particular factory, warehouse, or establishment in which electronic products are manufactured or held, may not be adequate or reliable, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are thereafter authorized (1) to enter, at reasonable times any area in such factory, warehouse, or establishment in which the manufacturer's tests *(or testing programs)* required by section 358(h) are carried out, and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, the facilities and procedures within such area which are related to electronic product radiation safety. Each such inspection shall be commenced and completed with reasonable promptness. In addition to other grounds upon which good cause may be found for purposes of this subsection, good cause will be considered to exist in any case where the manufacturer has introduced into commerce any electronic product which does not comply with an applicable standard prescribed under this subpart and with respect to which no exemption from the notification requirements has been granted by the Secretary under section 359(a)(2) or 359(e)."

(b) "Every manufacturer of electronic products shall establish and maintain such records *(including testing records)*, make such reports, and provide such information, as the Secretary may reasonably require to enable him to determine whether such manufacturer has acted or is acting in compliance with this subpart and standards prescribed pursuant to this subpart and shall, upon request of an officer or employee duly designated by the Secretary, permit such officer or employee to inspect appropriate books, papers, records, and documents relevant to determining whether such manufacturer has acted or is acting in compliance with standards prescribed pursuant to section 359(a)."

****

(f) "The Secretary may by regulation (1) require dealers and distributors of electronic products, to which there are applicable standards prescribed under this subpart and the retail prices of which is not less than $50, to furnish manufacturers of such products such information as may be neccessary to identify and locate, for purposes of section 359, the first purchasers of such products

NOTICE OF INSPECTIO

Exhibit 1
7/15/76
CK

SYNTEX RESEARCH, Toxicology Dept.
2349 Charleston Rd., Mt. View, Calif.

CHRONIC ORAL TOXICITY STUDY IN RATS WITH RS 3540

PURPOSE: To evaluate toxicity of RS 3540 given to rats orally for 6 months or 18 months.

PROCEDURE:

A. Animals

1. For this study use 140 ♂ and 140 ♀ Sprague-Dawley albino rats weighing 100 ± 10 gm. each.
2. Acclimatize animals to laboratory conditions for 1 week. This should include adaptation of the animals to ingestion of non-pelleted food.
3. House animals by sex 2-3 to a cage with food and water ad lib except as noted below.
4. Randomly assign 20 ♂ and 20 ♀ rats to each of four groups and 15 ♂ and 15 ♀ to an additional 4 groups.
5. Animal caging, quarters and care shall meet current Government Regulations.

B. Treatment

1. Animals are dosed daily by mixture of the test compound with food.
2. Adjust dosage weekly according to body weight and food intake.
3. Dose Groups:

Group	♂	♀	mg/kg/day RX	X Expected Human Dose	Treatment Duration (months)
100	20	20	---------	----------	18
100A	15	15	---------	----------	6
200	20	20	2.0	1	18
200A	15	15	2.0	1	6
300	20	20	10.0	5	18
300A	15	15	10.0	5	6
400	20	20	30.0	15	18
400A	15	15	30.0	15	6

Exhibit 1
7/15/76
CK

PROTOCOL NO.
Page 2.

C. Clinical Observations

1. General condition and behavior - daily.
2. Food intake (corrected for spillage) - weekly
3. Body weight - weekly.
4. Ophthalmoscopy - day - 7, 3 months, 6 months, 9 months, 12 months and 18 months. (Exclude from the study any animals with ocular abnormalities noted at the day -7 examination.)
5. At termination carry out slit lamp examination of 5 ♂ and 5 ♀ of each group.

D. Laboratory Analyses (All of high dose group and control, half of medium and low dose groups.)

1. Urine - once before dosing is started and quarterly thereafter.
   a) Place animals in metabolism cages and collect 24 hour urine samples.
   b) Measurements
      1) Volume
      2) Specific gravity
      3) Protein (semi-quantitative)
      4) Glucose (semi-quantitative)
2. Blood
   a) Draw blood samples terminally after overnight fast (all animals).
   b) Determinations (75% of high dose group, and controls, half of medium and low dose groups)*

hemoglobin	CA++	Bilirubin
hematocrit	Na+	Alkaline-phosphatase
WBC	K+	
differential cell count	SGOT	
platelet count	BUN	
clotting time	glucose	
**protein electrophoresis	LDH	

* Bleed all animals but freeze and store plasma from animals not analyzed at this time.

** 5 ♂ and 5 ♀ of each group.

Exhibit 1
7/15/76
CK

PROTOCOL NO.
Page 3.

E. Necropsy Schedule

1. Submit any animals that die to complete necropsy and determine the cause of death if possible.

2. Sacrifice all survivors at the end of the 6 month or 18 month treatment period as specified.

3. a) Examine all animals for gross pathological changes. At necropsy weigh and take for histologic examination: Pituitary, heart, liver, adrenals, kidneys, thyroid, ovaries or testes, uterus or prostate, and seminal vesicle. Also take for histology aorta, spleen, lungs, cervical and mesenteric lymph nodes, and representative portions of stomach, large and small intestine (duodenum, jejunum, ileum, cecum, colon) bone marrow, brain, mammary gland, bladder, pancreas, spleen and any other tissues with grossly evident lesions. Pay particular attention to the entire gastro-intestinal tract.

   b) Histopathological evaluation to be performed by contractor.

F. Reporting (Quarterly and at termination)

1. Text

   Report an assessment of the toxic effects, the general behavior and condition of the animals, body weights, food consumption, fatalities, laboratory findings, gross and histological pathology, organ weights and organ/body weight ratios.

2. Tables (by sex and dose group with averages and statistical evaluation)

   a) Individual body weights
   b) Average weekly food consumption
   c) Individual organ weights
   d) Individual organ/body weight ratios
   e) Individual laboratory findings (hematology, blood chemistries)

Exhibit 1
7/15/76
CK

PROTOCOL NO.
Page 4.

F. Reporting (Cont'd)

3. Graphs

Average body weights and food consumption by sex and dose group.

4. Excess wet tissues, tissue blocks and slides are to be forwarded to the sponsor.

G. Alterations

If, during the course of this study, any changes in this protocol appear warranted to the contractor, he should so notify the sponsor. No changes in this protocol may be made without written authorization by the sponsor.

Robert Hill, Ph.D.
Director of Toxicology

RH/ne

...L OF CLINICAL PATHOLOGY ... RESEARCH, STANFORD INDUSTRIAL PARK, PALO ALTO, CALIFORNIA 94304.

Exhibit 2
7/15/76
CK

November 18, 1971

Dr. Joe Calandra
Industrial Bio-Test
1810 Frontage Road
Northbrook, Illinois

RH-792

Dear Joe:

I am returning herewith for corrections and additional data a report prepared by your organization on a chronic toxicity study in rats with Syntex compound RS 3540.

I am very disturbed at the unsatisfactory nature of this report. It contains a large number of errors, discrepancies and omissions of data which I have indicated in red throughout the report. Data omitted was clearly requested in the original protocol (copy attached).

From past experience I am convinced that the report would be rejected by regulatory agencies in the U.S., U.K., Canada and Germany.

Would you please see that the report is corrected and returned at the earliest.

Very truly yours,

Robert Hill, Ph.D.
Director of Toxicology

RH:lc
Enclosures

Exhibit 3
7/15/76
CK

Industrial BIO-TEST Laboratories, Inc.
1810 FRONTAGE ROAD
NORTHBROOK, ILLINOIS 60062

AREA CODE 312
TELEPHONE 272-3030

TOXICOLOGY
ENVIRONMENTAL SCIENCES
CHEMISTRY
PLANT SCIENCES
MEDICAL SCIENCES

March 2, 1972

RECEIVED
MAR 3 1972
DR. HILL

Dr. Robert Hill
Director of Toxicology
Syntex Research
Division of Syntex Corporation
Stanford Industrial Park
Palo Alto, California 94305

Dear Bob:

Enclosed are three copies of revised pages 2, 3, 44, 46, 53, 54, 55 and 56 of the report of study IBT No. B7922 and copies of nine revised pages of the appendix. These pages have been revised to include the information contained in the histology addendum sent to you recently.

If there are additional questions, please call me.

Sincerely yours,

M. L. Keplinger, Ph.D.
Manager, Toxicology

MLK:psh
Enclosures

Associate Director for New Drug Evaluation July 20, 1976

Director
Scientific Investigations Staff

Naproxen, NDA 17-581

This transmits a summary of the findings of our recent inspection of Industrial Biotest Laboratories in connection with their 22-month rat study of Syntex' Naproxen. (A detailed report will follow when available.) We have concluded that this study is unreliable and should not be used in support of claims of safety for that drug. It has been determined that after the unreliable study is removed from consideration, NDA 17-581 does not contain adequate toxicologic data to support claims of safety for Naproxen.

We, therefore, recommend that procedures be initiated to remove Naproxen from marketing in this country.

Frances O. Kelsey, Ph.D., M.D.

cc:
HFD-2
HFD-100
HFD-150
HFD-108(2)
HFD-300
ABLisook/SIS/elf: 7/20/76
Endorsed by: MAGross 7/20/76
MMHein 7/20/76

Summary of Inspectional Findings made in Connection with 22-months Oral Administration Study Conducted in Rats by Industrial Bio-test, Northbrook, Illinois on NAPROXEN

Reference is made here to Industrial Bio-test (IBT) Study No. B7922 carried out for Syntex - number RS 3540-249-R-70-PO-TX, submitted by Syntex to IND 5281 for Naproxen on March 22, 1972.

According to the NDA 17-581 on this product, this represents the only long-term safety study, i.e. the only one carried out for a major portion of an animal's lifespan.

Following a recent inspection of IBT's laboratory records, we find this study unacceptable for the following reasons:

1) Lack of analytical documentation that the agent on test was actually incorporated in the experimental animals' diets at the prescribed concentration.

2) Indications that the experimental animals were either misidentified or misplaced among the various treatment groups:

   a) many animals recorded as having been weighed alive (some repeatedly) subsequent to the dates of their deaths;

   b) extreme body weight changes on successive weighings for given animals;

   c) extreme variation in body weight within any experimental group and controls at any given weighing;

   d) several animals being listed as having died repeatedly, usually with different versions of gross post-mortem findings;

   e) unaccountable discrepancies and corrections in dates of death of the experimental animals in different versions of same record or in different records;

3) A complete lack of any laboratory records in the areas of hematology, blood chemistry, ophthalmoscopic and slit-lamp examinations.

4) A partial lack of records on:

   a) body weight determinations (said to have been carried out weekly);

   b) urinalysis determinations;

   c) gross post-mortem observations;

   d) detailed histopathologic findings on all animals that died during the study;

   e) ante-mortem findings such as: presence of tumors, their site, size, general appearance and progress of growth, and the presence of other lesions and abnormalities.

5) Information submitted in the NDA report which is inconsistent with the raw data:

   a) average body weights at specified periods of time;

   b) gross observations found post-mortem;

   c) histopathologic observations;

   d) urinalysis results.

6) Other indications of poor practices in the pathology area:

   a) between 55% and 60% of the dead animals being in an advanced of autolysis;

   b) information on gross findings submitted to the examining pathologist which is at variance with that found in other records;

   c) failure to include in the report to Syntex all tumors and other lesions noted;

   d) inconsistencies between the detailed table on tumors and the summary table;

   e) lack of adequate professional supervision of technicians during pathology procedures;

   f) questionable, if not entirely inadequate, evaluation on safety of this product by pathologist.

7) Improper design of the study at least in the area of sampling animals for urinalysis; if the agent on test were to affect some of the animals in a progressive fashion, this could not have been clearly elicited or correlated with anatomical pathology findings.

8) Questionable averaging of results obtained from individual animals.

9) A general lack of documentation (dates and signatures or initials) by persons making entries or corrections in laboratory records of observations collected during this study.

It seems clear to us that the vast majority of the important findings listed above could not have been detected by review of the report prepared by IBT. However, it is felt that, particularly in view of the misgivings of Syntex on the initial version of this report (see enclosure) Syntex should have been more critical of the performance by their contractor; perhaps if Syntex had carried even an approximation of the sort of audit and examination of IBT's own laboratory notes as the FDA did, the report on this study would likely not have been submitted as a reliable one.

A separate overview on the regulatory aspects of this inspection will follow shortly.

M. Adrian Gross, D.V.M.

Manfred M. Hein

HFD-108/7-20-76

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 17-581

AUG 5 1976

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Harold C. Anderson, M.D.
Syntex Corporation
3401 Hillview Avenue
Palo Alto, California 94304

Dear Dr. Anderson:

Reference is made to your New Drug Application (NDA) for Naprosyn (naproxen) Tablets, NDA 17-581. Notice is hereby given that the Food and Drug Administration intends to publish in the Federal Register a Notice of Opportunity for a Hearing on our proposal to withdraw approval of your NDA for this drug. Such action is being taken pursuant to 21 CFR Section 314.115 because (1) we have reason to believe that the application contains an untrue statement of a material fact and (2), thus, the drug may be unsafe for use under the conditions of use upon the basis of which the application was approved. Dr. Carter's letter of July 23; 1976 to Dr. Finkel requested an opportunity to meet with us to discuss the 22 month rat study before any final recommendations ensue from the Bureau. Accordingly, before we publish such a Notice your request will be honored. You may also wish to present any additional information you may have bearing on the safety data for naproxen.

Specifically, our proposed action is based upon a recent inspection by FDA scientists of the conditions of performance and the laboratory records of the 22 month rat study carried out for your firm by Industrial Bio-Test of Northbrook, Illinois. The results of this study were submitted by you in your NDA in partial fulfillment of the requirements to establish, by substantial evidence, the safety of naproxen. [21CFR §314.1(c)(2)]. Our scientists concluded that this study is unacceptable for the following reasons:

1. Lack of documentation that analyses were performed to assure that the agent on test was actually incorporated in the experimental animals' diet at the prescribed concentration.

2. Indications that the experimental animals were either misidentified or misplaced among the various treatment groups:

a. Many animals recorded as having been weighed alive (some repeatedly) subsequent to the dates of their deaths;

b. Extreme body weight changes on successive weighings for given animals;

c. Extreme variation in body weight within any experimental group and controls at any given weighing;

d. Several animals being listed as having died repeatedly, usually with different versions of gross post-mortem findings;

e. Unaccountable discrepancies and corrections in dates of death of the experimental animals in different versions of the same record or in different records.

3. A complete lack of any laboratory records in the areas of hematology, blood chemistry, ophthalmoscopic and slit-lamp examinations.

4. A partial lack of records on:

a. Body weight determinations (said to have been carried out weekly);

b. Urinalysis determinations;

c. Gross post-mortem observations;

d. Detailed histopathologic findings on all animals that died during the study;

e. Ante-mortem findings such as: presence of tumors, their site, size, general appearance and progress of growth, and the presence of other lesions and abnormalities.

5. Information submitted in the NDA report which is inconsistent with the raw data:

a. Average body weights at specified periods of time;

b. Gross observations found post-mortem;

c. Histopathologic observations;

d. Urinalysis results.

6. Other indications of poor practices in the pathology area:

a. Between 55% and 60% of the dead animals being in an advanced state of autolysis;

b. Information on gross findings submitted to the examining pathologist which is at variance with that found in other records;

c. Failure to include in the report to Syntex all tumors and other lesions noted;

d. Inconsistencies between the detailed table on tumors and the summary table;

e. Lack of adequate professional supervision of technicians during pathology procedures;

f. Questionable, if not entirely inadequate, evaluation on safety of this product by the pathologist.

7. Improper design of the study at least in the area of sampling animals for urinalysis; if the agent on test were to affect some of the animals in a progressive fashion, this could not have been clearly elicited or correlated with anatomical pathology findings.

8. Questionable averaging of results obtained from individual animals.

9. A general lack of documentation (dates and signatures or initials) by persons making entries or corrections in laboratory records of observations collected during this study.

The Bureau of Drugs' recommendations for animal toxicity studies in support of approval for marketing of a compound to be given six months or longer in clinical practice include an 18 month study in a rodent and a 12 month study in a non-rodent. Such a policy has been enunciated in various speeches between 1968 and 1972 by Dr. William D'Aguanno, Chief Pharmacologist of the Bureau of Drugs, and in his publication entitled "Drug Toxicity Evaluation--Pre-Clinical Aspects" (See "FDA Introduction to Total Drug Quality," U.S. G.P.O. No. 1712-00220; also, Industrial Pharmacology, Vol. 1, pp. 317 ff., Futura Publishing Co. 1974.)

In the absence of a long-term rodent study we are not able to evaluate the chronic toxic effect of the compound or make a proper assessment of carcinogenic potential of the agent.

Neither of the other long-term animal toxicity studies conducted for 12 months in the mini-pig (also by Industrial Bio-Test, albeit in a facility other than the one in which the rat study was conducted) and 39 weeks in the rhesus, is entirely satisfactory for the determination of chronic toxicity since neither was carried out over the major portion of the life span of the animals and, because of this, neither is satisfactory for determination of carcinogenic potential. In addition the limited number of animals studied would also preclude a meaningful assessment of carcinogenic potential. For the same reasons clinical trials to date would not be sufficient to determine long-term toxicity or oncogenic potential.

We should like to point out that our scientists observed serious deficiencies in the Industrial Bio-Test study as a result of only a half-day of inspection, although their in-depth analysis of the records did, of course, require several weeks. The deficiencies could also have been readily detected by your firm and we are disappointed that no attempt was made to monitor and audit such an obviously crucial study in support of the safety of your drug.

88-938 O - 77 - 6

Please respond within 7 days either by phone (301-443-2895) or letter if you wish to meet with us to discuss the above issues.

Sincerely yours,

J. Richard Crout, M.D.
Director
Bureau of Drugs

cc:
NDA-17-581
HFD-1
HFD-2
HFD-150
HFD-108
HFD-100
GCF-1
MJFinkel:ih/7/30/76

R/D initialed by:		
	C. M. Leventhal	7/28/76
	W. D'Aguanno	7/28/76
	A. Gross	7/29/76
	W. Gyarfas	7/28/76
	M. Hein	7/29/76
	A. Norris	7/28/76

Re-initialed by R. Parker
as typed by R. Merrill 7/30/76

M. J. Finkel 8/2/76

MEMORANDUM

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

TO : Mr. Dale Stelter, Investigator
Waukegan Resident Post
Chicago District Office

DATE: AUG 10 1976

FROM : Manfred Hein, HFD-150
M. Adrian Gross, HFD-108

SUBJECT: Technical Review of Data to be appended to Establishment Inspection Report (6/21-24, 1976)

Industrial Biotest Laboratories (IBT) Study No. B 7922 carried out for Syntex Laboratories, Palo Alto, CA on Naproxen (RS 3540 - 249-R-70-PO-TX) submitted to IND file 5281 and NDA 17-581, approved March, 1976.

This study represents the only long-term rodent trial carried out for this product according to information available to HFD-150. It was intended as a chronic toxicity and/or carcinogenesis study and it was apparently carried out at IBT between 11/25/69 and 9/17/71, the last being the date noted for the killing of all surviving animals. The IBT report to Syntex on this multi-level oral administration study in rats is dated January 4, 1972 and the copy submitted to the IND file is stamped "Received" at Syntex on March 3, 1972. Syntex submitted this to their IND file under cover letter dated March 22, 1972. It is appended here as Exhibit A.

At the time of the inspection we requested all records of original data and observations collected in connection with this study; we were provided with the following:

Body-weight records collected on individual animals periodically	Appended here as Exhibit B
Food consumption records used in the calculation of the dosage administered	Copies of these were not collected
Records of urinalysis determinations	Appended here as Exhibit C
Records of gross observations made at the post-mortem examination of the animals	Appended here as Exhibit D
Records of organ weights collected at the post-mortem examination of the animals	Appended here as Exhibit E
Alternate records of organ weights collected at the post-mortem examination of the animals	Appended here as Exhibit F
Computer-generated records of organ weights collected at the post-mortem examination of the animals	Appended here as Exhibit G
An original running log of gross post-mortem lesions seen in each animal in chronological order of deaths	Appended here as Exhibit H
A corrected version of the above	Appended here as Exhibit I
A record of the results of histopathologic observations made by Dr. Wade Richter of the University of Chicago Medical School, who acted as the consulting examining pathologist	Appended here as Exhibit J
A compilation of times of death, gross and microscopic lesions for each animal in the study prepared by Mr. James Plank of IBT; this was appended to the IBT report to Syntex and submitted by Syntex to the FDA; although properly a part of Exhibit A, we chose to have it appended here.	Appended here as Exhibit K
The protocol for this study was submitted to the NDA; since it is material for our discussion, it is appended here	Appended here as Exhibit L

In addition to these, we were shown and given a copy of a letter of transmittal from IBT to Syntex of all tissue sections and paraffin blocks collected in connection with this study.

We were told that the following could not be found despite a determined effort at searching and despite the fact that they probably existed during the course of the study:

Body weight records for each of the first eight weeks of the study and for several weighings thereafter

Any laboratory records of hematologic determinations

Any laboratory records of blood chemistry determinations

Any laboratory records of periodic ophthalmology examinations or of the terminal slit-lamp examination

For the 160 animals allegedly in this study, we were given records of gross pathology examination for only 30 animals (Exhibit D); Mr. Plank explained to us that for the 44 animals killed at the end of the study no such records were prepared; however, this still leaves 86 (approximately 54%) animals which died during the study for which no such records were made available to us; we were told these could not be located.

We were also told that no records were kept on the actual level of the test drug in the diet of the animals as ascertained by chemical analysis; the reason for this is that no such determinations were ever made and this was due, we were told, to the IBT contract with Syntex not specifically providing for such analyses.

An important general point to be made at the outset is that in only a very few instances did technicians or professionals making records of observations sign or initial and date entries of their findings.

Ante-mortem Observations of the Animals in the Study

Although the study protocol (Exhibit L) provides for daily observation of the "general condition and behavior" of the animals, no specific records of such observations were provided for us despite our repeated enquiries into this problem.

However, some of the body weight records (Exhibit B) - but largely only those collected during the 4th month and those collected from the 14th through the 17th month of the study - do have certain indications referring to inner ear infection, the presence of diarrhea, unspecified sickness of the animals or the development of tumors. The tumors in these observations were not further characterized as to their location, size, rate of growth or general appearance. Interestingly, such entries on the presence of tumors are virtually absent after the 17th month of this 22 month study.

In only one case was an externally visible lesion other than a tumor noted: this was a high-level female (no. 160) for which on 3/6/70 a "sore on the side" was indicated on the body weight record made on that date; at the following weighing on 3/13/70 a similar entry was made for another animal in this group, no. 159, and no entry is made for animal no. 160 at that date.

The body weight records in Exhibit B indicate that on 1/21/71 two high dose females (nos. 144 and 152) developed unspecified tumors; at the next weighing on 2/4/71 the "tumors" in these animals were apparently no longer observed; however, two other animals in this group (nos. 146 and 157) are said to have tumors at that time and for these the tumors are said to have continued to be observed at other subsequent observation times.

In the low dose group one male (no. 47) and one female (no. 63) each are said to have tumors on 3/10/71 but not at any other time of ante or post-mortem observation and no other records on such lesions exist for the gross or microscopic examinations for these animals.

There are many entries on ante-mortem body weights of the test animals recorded for dates at which other records indicate the animals have been dead for some time. Below are merely a few examples limited to the control group of animals even though this problem is extensive throughout the entire study:

Sex	Animal Number	Date animal is first indicated as being dead	Subsequent date of first ante-mortem body weight entry	Number of additional ante mortem body weight entries
M	4	01/21/71	02/04/71	0
	12	05/15/71	05/24/71	8
	13	04/06/71	05/15/71	0
	15	10/26/70	02/04/71	12
	16	02/04/70	06/23/71	1
	20	03/18/71	06/01/71	4
F	21	06/01/71	07/27/71	0
	29	09/28/70	06/01/71	1
	31	10/05/70	04/21/71	0
	32	04/21/71	04/27/71	10

It is quite likely that this problem arises due to failure to clearly identify each animal (ear-punch, toe clip, etc.) and that, as a consequence of this, animals were switched from cage to cage in an unknown manner, i.e. they were misplaced. Indications that this was a widespread problem at least in this particular study can be provided by the variability of recorded weights of individual animals for some of the successive weighings (see Exhibit B). Again, merely a few examples limited to the control group only:

Animal Number	Date & weight (gms.)	Date & weight (gms.)	Date & weight (gms.)
27	07/16/71 - 555	07/27/71 - 370	08/09/71 - 590
34	10/05/70 - 390	10/12/70 - 598	10/20/70 - 403
13	10/05/70 - 528	10/12/70 - 450	10/20/70 - 538
35	03/06/70 - 345	03/13/70 - 263	05/06/70 - 320

Again, this kind of discrepancy was noted throughout the length of the study and in all experimental groups.

In addition to this kind of extreme variation in the body weight of any given animal with time, there appears to be marked variability amongst the body weights of animals in any given experimental group at any given weighing. This also could be indicative of the possible misplacement of the animals in this study and, as an illustration, the following are highlighted here from merely the control group at only two weighings:

Weights in grams of control animals at two weighings (see Exhibit B) - (We have underlined the lowest and the highest weights in each group to emphasize the range)

Weighing on 06/23/71		Weighing on 10/05/70	
Males	Females	Males	Females
765	339	658	392
745	350	612	328
859	547	703	318
785	439	660	589
780	460	803	435
609	475	743	332
808	370	770	407
560	455	625	355
605	670	680	292
814	390	670	390
750	634	790	558
646	705	528	357
		516	462
		800	323
		855	483
		688	
		660	
		603	
		647	

According to the protocol for this study (Exhibit L) there should have been weekly weighings of the animals; for the 22 months of the study this would represent approximately 100 such weighings; we were given records on only 32 of the weighings with the balance of these being said to be not available. The missing records have reference to the first eight weeks of the study with the remainder representing gaps of up to four months (from the 6th to the 10th month) of the study. However, the report IBT submitted to its client, Syntex, (which, in turn submitted this report to the FDA) contains group means of such weighings for each of the first 13 weeks of the study and for each subsequent month thereafter.

It is clear to us that none of these problems could have been appreciated by any reviewer of the report, either at Syntex or at the FDA, since the report gives no details on the body weights of individual animals and not even a measure of variability such as the range, variance, standard deviation or standard error.

Such means of the body weights as were reported by IBT to Syntex (which submitted the report to the FDA) were largely inconsistent with the equivalent means discovered by us in the original records we inspected at IBT. Again, only a brief example limited to merely three weighings out of the nearly 100 supposed to have been carried out in this study:

Original body weight records (Exhibit B) disclose the following means: (weights in grams)

	MALES			FEMALES		
mg/kgm group	8 wks. 1/20/70	9 wks. 1/30/70	12 wks. 2/20/70	8 wks. 1/20/70	9 wks. 1/30/70	12 wks. 2/20/70
0	401	429	474	257	270	287
2	399	433	486	246	267	283
10	405	440	490	254	267	281
30	389	419	476	247	261	270

Report submitted to FDA (Exhibit A) discloses the following means (gms.) for each sex and for the time periods as listed in the columns above:

0	321	364	454	225	238	281
2	341	375	460	220	231	275
10	341	374	462	219	230	270
30	340	367	455	210	221	260

It is clear that there seems to be little if any relationship between these two sets of means which are supposed to be identical. We asked Mr. Plank of IBT who was the person who prepared these tables in the final report, but he seemed vague on this subject and could not recall exactly who this might have been beyond the fact that it was probably some technician. As can be seen on page 4 of Exhibit A, Mr. Plank, the Senior Group Leader of something called Rat Toxicity at IBT, approved this report.

Clinical Pathology Procedures

As mentioned earlier, although the study protocol (Exhibit L) and the final report submitted by IBT have reference to hematologic determinations and to blood chemistry assays of various sorts, the firm could produce for us no evidence whatsoever in the form of original laboratory records that these were actually carried out.

As for urinalysis procedures, the study protocol called for determinations on all high level and control animals and on half of the remaining animals (10/sex/group) in the study. The final report (Exhibit A) indicates that only five animals of each sex in each group were utilized for this purpose. The original laboratory notes (Exhibit C) however, disclose that 10 animals of each sex in each group were actually used. Lest one conclude that criticism on this point is not warranted (since it is more reliable to conduct tests on a large rather than on a small sample) it may be worth mentioning that the report indicates only the mean values of these periodic urinalysis determinations. If one is led to believe that these means are based on samples of five animals (as the IBT final report does), but in reality they are carried out on samples of size ten, the variability or

standard deviation of such means will be automatically reduced by a factor of square root of two; thus the point can be made that the means will show less variability with time at least partly due to the fact that a reviewer is being misinformed on the true size of the sample on which such means are based.

Mean values derived from readings on individual animals are questionably computed particularly with reference to albumin and globulin on which occasional animals show trace or positive values. Even when the readings are strictly numerical (as in the case of the urine volume) some of the values presented in the final report (Exhibit A) are false when viewed against what the laboratory notes indicate. For example, at 3 months the mean volume of urine for 24 hours for the medium-level males is indicated in Exhibit C to be 14.5 ml but reported in Exhibit A to be 15.9 ml. Similar inconsistencies between means computed in the laboratory and those reported by IBT occur for the specific gravity of the urine of high level males at 3 months, and for both albumin and glucose of high-level females and of control animals at 9 months.

Although the final report of IBT (Exhibit A) refers to urinalysis determinations at 22 months of the study, there is no evidence in the form of laboratory notes that these were actually carried out.

The study protocol (Exhibit L) called for baseline urinalysis of the animals before exposure to the test agent was initiated. This was not carried out.

Perhaps the most important impropriety of the urinalysis determinations is that although these were carried out approximately four times a year, not necessarily the same animals were used each time; even if the same animals were used, one cannot put sequential readings into any correspondence with any given animal. Thus, if the test agent were to affect the urinary tract of some of the animals in a given tretament group and if this effect were non-reversible or progressive with time, there would be no way such manifestation of toxicity could be clearly elicited or related to any anatomic lesions discovered on pathologic examination.

Since the inspection at IBT was completed we have requested by telephone from Syntex a list of all sections of tissue from this study which had been received there from IBT. This was provided for us by Syntex under cover letter dated July 20th, 1976 and it is appended here as Exhibit M.

Disposition of the animals in this study

Comparison of Exhibits H and I reveals that a copy of the original log of gross observations had been corrected at a subsequent date. Although we asked for the circumstances or justifications for these corrections at IBT during an interview with Mr. Plank, he could not clarify these for us. What are some of these corrections ?

Original Version (Exhibit H)	Corrected Version (Exhibit I)
Animal 136 the date of whose necropsy is given as 12/08/69 is said to be TBD/TDA meaning "too badly decomposed/ technician destroyed animal."	The entire entry for this animal has been struck through with a wavy line as if no information on this animal is available.
Animal no. 360 in this study is listed together with a date for its necropsy- there were only 160 animals in this study and they were numbered sequentially from 1 through 160.	The number of this animal is struck through and is replaced by a new number - 160 - followed by a question mark.
Three animals - Nos. 109, 24, & 25 - have a symbol of "p" in front of their numbers.	The 3 symbols are missing here.
Although, as explained, there were 160 animals in this study numbered uniquely from 1 through 160, the original version has reference to animal no. 87 having been examined post-mortem on 3/3/71; two lines below this entry there is another entry for animal 87 having been examined post-mortem eight days later - 3/11/71; to distinguish these two a notation of "a" and "b" had been placed opposite these entries.	The "a" and "b" are gone here; the number 87 has been left unchanged in both entries but the second entry is now followed by a question mark.
Animal 102 is said to have been examined post-mortem on 6/24/71 at which time a maximum score of 4 has been given to the state of decomposition of its carcass. No grossly observable lesions or other marks are noted for this animal; seven lines below this entry the same animal is said to have been examined post-mortem 36 days later when the score for decomposition of the carcass in only 3 and this time the animal is reported to be a "mis-sexed female, marked male". The animal is also said to have pneumonia scored with a severity of 3 and the stomach is noted as being hemorrhagic. The two entries have been distinguished by the symbols "a" and "b".	The "a" and "b" distinctions are not present here but the second entry has been supplemented by a question mark; all other inconsistencies are left unresolved.

Certain information is given on animal no. 54.	The number of this animal has been corrected to 58.
Twelve females from the low-level group are listed as having been killed at the termination of the study; the list does not include animal no. 73.	13 such animals, including no. 73 are listed here as having been killed terminally from this group.
Animal no. 20 is listed as having been examined post-mortem on 3/11/71 when no lesions or other remarks are noted except for the carcass being too badly decomposed and that the technician destroyed the animal; almost five months later (8/3/71) this animal died again when the state of decomposition of its carcass rates only a score of 2, but this time its lungs are described as being hemorrhagic (grade 3), the mesenteric nodes congested with blood, the pituitary has an adenoma the size of a large pea and there are two tumors: one in the right axillary region and one in the lower left abdomen.	None of these discrepancies were corrected in the revised version of this record.
Animal no. 40 is said to have suffered a "bleeding death" meaning that it died accidentally during bleeding. The date of death or post-mortem examination is not given and neither is it given in the pathological observation sheet for this animal (one of the few that were made available to us). However, the weight records on this animal (Exhibit B) indicate that this animal probably died between 1/30/70 and 2/20/70, i.e. at a very early stage of the study. But no "bleedings" were carried out at times other than the conclusion of the 22 months observation period.	The mysteries associated with this animal are not clarified in the corrected version of this record.

Animal No. 119 is said to have been presented for necropsy on 6/2/71 at which time it was said to be "too badly decomposed and no tissues were taken." Two and a half months later presumably this animal died again since the necropsy dated 8/18/71 disclosed that the state of decomposition of its carcass is now only a grade 4 (there is no notation of the technician having destroyed the animal) and the lungs this time are described as being hemorrhagic (grade 3).	The corrected version of this record again is not helpful here.
Animal No. 122 is listed as having been examined post-mortem on 7/30/71 and there are no remarks either on the state of decomposition of its carcass or on any gross lesions being present. Another entry on another page of the same record again lists this animal for the same date - 7/30/71 - but here the state of its decomposition is rated as 3 and also there are notes on fatty degeneration of the liver, a rather marked pneumonia and a rather marked pneumonia and a hemorrhagic stomach.	The same inconsistencies are still present in the corrected version of this record.
The first item considered here was animal no. 136 which was noted as having been examined post-mortem on 12/8/69; another entry in the original version of this record lists this animal as having been examined post-mortem on 2/15/71 or more than 14 months later.	As mentioned above, in the corrected version of this record the entry was entirely struck through with no additional explanations; the second entry is left unchanged in the corrected version. In response to a question from us. Mr. Plank of IBT volunteered the opinion that following the death of the original animal numbered 136, another animal was substituted for it and given the same number. He could not point out any written record to this effect.

In addition to the inconsistencies between two versions of the same record we are presenting below some examples of other inconsistencies relating to dates of death of the animals in this study. This time, however, we shall additionally address the matter of possibly false information submitted to the sponsor (Syntex) which caused the latter to submit such possibly false information to the FDA in support of an IND and an NDA. Again, this

does not constitute an exhaustive list of all such irregularities, but merely a set of a few examples which we judge to be sufficient to allow one to draw some conclusions on the quality of this work.

In the following list, where we compare entries made in a variety of records, we shall have reference to ante-mortem body weights collected at certain dates (Exhibit B), the gross observations made at the time of necropsy of these animals as indicated in Exhibit D, the log of such observations (Exhibit H) which, we were told, is based on the sheets given under Exhibit D, the information given by IBT to their consulting pathologist, Dr. Richter (Exhibit J) and, finally, Exhibit K which, as stated at the outset here, represents the compilation which IBT submitted to Syntex in their final report and which Syntex, in turn, submitted to their IND file and to their NDA.

Control Males

Dr. Richter was given the time to death of only two of the twenty animals in this group: No. 18 which is said to have died after 4 months and No. 20 which is said to have died after 2 months. Information sent to the FDA indicates animal No. 18 to have died after 21 months, and for animal No. 20 no time to death whatsoever is given. There are no pathology sheets for 17 out of the 20 animals in this group and the log record does not acocunt for the time to death or date of death for 5 of the 20 animals: Nos. 2, 6, 7, 8, and 15. Pathology sheets for all five of these animals are also missing. No time to death is given in the final report (Exhibit K) for animal No. 15. For animal No. 2 there is no original entry of date of death but the final report indicates 9 months to the death of this animal; the body weight records, however, indicate that this animal was alive on

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10/26/70, 11 months into the study. Essentially the same is true of animal no. 7 reported to the FDA to have died after 16 months or near the end of March, 1971; body weight records, however, indicate this animal to be alive as late as 7/27/71. An even more glaring discrepancy exists for animal No. 9 which is said to have died after 19 months in the final report; but both the pathology sheet on this animal and the log book indicate a death after less than 7 months.

Control Females

Dr. Richter was given the time to death of none of the 20 animals in this group. There are pathology sheets on only 3 of these animals and the log notes omit any reference to animals no. 21, 29, and 38. The information submitted to the FDA contains among other things: that animal no. 21 survived only to 6 months when body weight records indicate it was alive on 7/27/71 (some 20 months of the study); that animal no. 23 survived to 16 months when the log notes indicates necropsy on 3/24/70 (some 4 months of the study); that animal no. 26 survived to 14 months when three other records (Exhibits B, D, and H) all indicate death in January 1970 (less than 2 months of the study); that animal no. 38 survived to only 12 months when Exhibit B indicates a body weight being recorded on 4/27/71 (some 17 months into the study).

Low Level Males

Dr. Richter was given the times to death of only 3 of the 20 animals in this group and it is interesting to compare these with what is reported to the FDA:

Animal No.	Information to Dr. Richter by IBT (Exhibit J)	Final Report by IBT (Exhibit K)
51	4 months	12 months
55	4 months	11 months
59	3 months	20 months

There are pathology sheets for only 3 of the 20 animals in this group and the log omits any reference to animal nos. 42, 43, 47 and 49, all of which have missing pathology sheets. Yet for each of these a definitive time to death is reported by IBT; one wonders what is the source of such information and how reliable it is. For animal no. 49 the time to death in the final report is given as 20 months yet the body weight records for this animal indicate no measurements after 10/26/70 - 11 months into the study.

The discussion above covers only 3/8 or slightly more than one-third of the animals in this study; essentially the same problems exist with the other 5/8 of the animals, but it would serve little to give any additional exhaustive details on these.

Pathology Operations

A. The matter of decomposition of carcasses

There are 96 entries for dead animals in the running log of pathology observations (Exhibit H) and 43 or 44 entries for survivors killed at the end of the 22 months observation period. Their sum falls somewhat short of the total of 160 animals in this study - many animals are not accounted for whatsoever and several instances of multiple entries exist for the same animal as has already been demonstrated here.

From among the 96 entries for dead animals, only 22 have no notes on some kind of decomposition state of the carcass; 18 are graded with a score from 1 to 4 on the severity of such decomposition (14 with a score of 3 or 4) and 55 of these 95 entries, or approximately 58%, carry a note "TBD" meaning "too badly decomposed."

If this kind of information were disclosed in the report prepared by IBT which was submitted to the FDA (and we would properly expect this sort of thing to have been so disclosed), it would have been sufficient to invalidate this study as pathology practices such as these are completely unacceptable.

For all but 7 of these 55 entries marked TBD, there is the companion note TDA meaning "technician destroyed animal"; for the balance of the 7 cases there is the notation NTT meaning "no tissues taken" which indicates that no tissue sections for histopathologic examination were collected. Yet for two of the animals with this particular notation (NTT) - nos. 119 and 22 - results of histopathologic observations are given in the report submitted to the FDA (see Exhibit K). As to what animals are actually the source of the tissues represented as belonging to numbers 119 and 22 is anyone's guess.

For those 48 entries marked "TBD/TDA" it can be reasonably expected that a less than complete necropsy examination was carried out and that any abnormalities observed would have to be modified by the advanced state of decomposition of the carcass. These expectations,

however, did not deter IBT from presenting in the final report submitted to the FDA a list of grossly observable lesions in these animals. No mention whatsoever is made there of the advance autolytic changes. We do not know of any pathologist who would be as bold as to state that an animal has "pneumonia" or pulmonary "congestion" given that a carcass is "too badly decomposed" since often autolytic or hypostatic changes mimic these very same conditions. We are also wondering as to what pathologist made such diagnoses in these animals given that the "technician destroyed animal," a notation present for 48 of these 55 entries. The following is a list of only some of these animals: numbers 82, 90, 85, 50, 5, 117, 133, 45, 16, 157, 103, 13, 76, 89, 136, 148, 23, 31, 144, 41; they represent examples from all eight experimental groups - four treatment levels (including controls) for each of the two sexes.

B. The unreported tumors and suspected tumors

Even more serious are instances where either or both the post-mortem pathology sheet (Exhibit D) and the running long (Exhibit H) of animals dying during the study with important lesions disclose the presence or suspected presence of tumors. Yet no such information was given to the pathologist who examined the tissues (Exhibit J) and his report on histopathologic observations makes no mention of any such lesions or IBT did not provide such information in the final report to Syntex which the latter submitted to the FDA. Examples:

a) A pituitary gland adenoma for animal No. 59 (a low-level male) which is also said to have had thyroid glands "enlarged 2x" (Exhibit H): the latter may indicate the presence of yet another tumor.

b) animal No. 20 (a control male) is said to have had a pituitary adenoma the size of a large pea (Exhibits H, I and D); yet no information on this is given to the pathologist (Exhibit J). From whatever sections (allegedly from this male animal) were sent to the pathologist for examination, he concluded this was a female animal (Exhibit J). The list of these sections sent to us by Syntex (Exhibit M) includes ovaries. Yet IBT's report to Syntex (Exhibit K) prepared after receiving the pathologist's report, clearly indicates this animal to be a male and makes no mention of either the pituitary adenoma or of the mammary adenocarcinoma noted for it. The tumor table for individual animals (page 58, Exhibit A) does list the adenocarcinoma of the mammary gland, but not the pituitary adenoma and it attempts to maintain the fiction the tissues from this animal were those of a male. A second externally visible tumor (Exhibit H) is not reported upon by IBT.

c) Another example of a pituitary adenoma which was observed grossly but not reported either to the pathologist or in the final report submitted by IBT(Exhibits A and K) was in animal No. 18. No sections whatsoever for this animal were sent to the pathologist.

d) Animal number 111 (a mid-level female) is reported by the pathologist (Exhibit J) to present a mammary adenocarcinoma. This information was withheld by IBT from its final report (Exhibit K and Exhibit A - detailed tumor table).

e) Animal number 66 is indicated (Exhibit H) to have had a large fibrous tumor in the lung "affecting all left lobes, 23.95 gms." The same is given in the post-mortem protocol (Exhibit D). No

mention is made in either of these two records of any mammary tumors. Hoever, no information on any lung tumors is given to the pathologist (Exhibit J) who, amazingly, reports for this animal a ...mammary fibroadenoma. The final report prepared by IBT (Exhibits A and K) refers only to the mammary tumor.

f) A splenic tumor and extramedullary hematopoiesis are indicated by the pathologist (Exhibit J) for animal 149 (a high-level female) and this also appears in the final report (Exhibit K) but the tumor table on page 59 (Exhibit A) indicated that extramedullary hematopoiesis itself is a tumor, an unacceptable finding.

g) A possible tumor to the left adrenal was present in animal 25 (a control female) which in Exhibit H is said to be enlarged three times the size of normal. The final report prepared by IBT (Exhibit K) does not mention even the grossly observed change.

h) A pituitary adenoma was indicated for animal No. 109 (a mid-level female), This was not verified microscopically, and no information on this tumor appears in the tumor table (page 59 of IBT's final report (Exhibit A).

i) A lymphatic tumor weighing 4.5 gm is indicated for animal 140 (a high level male) on Exhibit H. The pathologist reports

on microscopic examination a thymoma (with a question mark) for this animal (Exhibit J) but no information on the lymphatic tumor observed grossly is given to him. The final report produced by IBT carries no mention of either the lymphatic or the thymic tumor in Exhibit K and only of the unconfirmed lymphatic tumor in Exhibit A.

j) Pituitary tumors may have existed in a number of the surviving animals - none of these were reported by IBT in Exhibit A - where the table of individual tumors is presented on pages 58-59:

Animal No.	Notes in Exhibit H
1	pit. enlarged 5x
12	pit. adenoma 10x
17	pit. adenoma
30	pit. adenoma +1
33	pit. ad. 2x
35	pit. ad. +2
98	pit. enl. 3x

The pathologist was not informed of the grossly visible changes in any of the seven instances above and no results of histopathologic observations are given in any of these cases. Another unsettling observation to be made here is that for this set of survivors as many as 5 of only 16 (31.25%) control animals are said in Exhibit H to have pituitary adenomas but only 1 of 27 or 28 (3.7% or 3.35%) treated animals are in this category, a reduction approximately 8.5-fold.

k) For animal 77 (a low-level female) <u>three</u> externally visible tumors

are indicated in the log(Exhibit H). Only one of these tumors, however, is reported in IBT's final report (Exhibits A and K).

l) A mammary tumor measuring 1x1x½" is reported in the left abdominal region of animal No. 110 (a mid-level female) - see Exhibit H. No information or tissue on this tumor was conveyed to the pathologist (Exhibit J) but Exhibit K does mention the presence of this tumor. However table XXXII on pages 58-59 of the final report (Exhibit A) has no reference to this particular lesion.

m) The mesenteric lymph nodes are mentioned in the log of pathology (Exhibit H) to be "swollen 100 x normal or more" (a feature almost beyond belief) and the spleen enlarged +2 for animal No. 152 (a high-level female). This sounds suspiciously like a multicentric lymphoid tumor, likely malignant. Yet the pathologist's report (Exhibit J) is silent on both the gross and the microscopic features of this lesion and so is the final report (Exhibits A and K).

n) A lymphosarcoma of the lung is reported for animal 83 (a mid-level male) in Exhibit K but not in Exhibit A of the final report.

o) A tumor-like growth in the lung is reported (Exhibit K) only grossly for animal 127 (a high-level male). No mention of this appears in the final report (Tumor table, pp. 58-59, Exhibit A) and no information on this or any tissue sections were sent to the pathologist (Exhibit J). Syntex has no slides on this animal (Exhibit M).

C. Mere examples of other irregularities in reporting pathology observations.

a) None of a multitude of gross abnormalities described in Exhibit H for animal 59 (a low-level male) were reported to the pathologist (Exhibit J) and only a portion of these is reported in the final

report (Exhibit K), some incorrectly.

b) Essentially the same is true of animal 122 (a high-level male).

c) No gross lesions are reported in the final report (Exhibit K) for animal 118 (a mid-level female) even though some are indicated in Exhibit H. Exhibit J also makes no mention of these; in the latter it is also implied that the esophagus, the pituitary gland and the salivary gland were not examined microscopically since a straight line is drawn through the space for each of these; Exhibit M however discloses that sections of these three tissues were in fact prepared.

d) Exhibit H discloses that no gross changes were noted for animal 94 (a mid-level male); yet the final report by IBT (Exhibit K) indicates this animal to have had pneumonia.

e) The gross lesions indicated in the IBT final report (Exhibit K) for animal No. 20 (a control male) are much fewer and different than those given in the internal records found at IBT (Exhibits H and D); Exhibit K has reference only to pneumonia whereas Exhibits H and D do not indicate pnuemonia but rather severe hemorrhage in the lungs, mesenteric lymph nodes congested, pituitary adenoma the size of a large pea and two tumors, one in the axillary region and one in the abdominal region.

f) For animal 86 (a mid-level male) the pathologist's report (Exhibit J) indicates severe autolysis, chronic focal myocarditis, periarteritis in the tongue, pyelonephritis and inflammation of the prostate with the trachea, esophagus, the pituitary, adrenal and salivary glands being indicated as not having been examined; the

IBT final report however (Exhibit K) refers to the myocarditis, the prostatic inflammation, and the periarteritis, but not to the pyelonephritis or to the sections not examined; in exchange, apparently, it also indicates a grade 3 chronic respiratory disease in the lung as well as erosion and calcification in the stomach, none of which were recorded by the pathologist.

g) For animal number 18 (a control male) we have the following comparison:

Internal IBT records (Exhibit H)	Report submitted to FDA (Exhibit K)
lungs - pneum. +3 consol. +3	lungs - pnuemonia
pit. - slt. ad. - bloody left ear - inner ear infection	

h) For animal number 22 (a control female) we have another comparison:

Internal IBT records (Exhibit H)	Report submitted to FDA (Exhibit K)
Gross Too badly decomposed No tissues taken	Gross Lung - hyperemia Lymph nodes - congestion Adrenal glands - enlarged
Histopathologic Despite the note that no tissues were collected for histopathologic examination, that there is no report on histopathologic observations by Richter (Exhibit J), and that the list of sections sent by IBT to Syntex indicates no such sections for this animal (Exhibit M)	Histopathologic Chronic tracheitis Chronic respiratory disease Chronic nephritis

i) For animal No. 87 (a mid-level male) no grossly observable lesions are recorded in IBT's own records (Exhibit H) yet the final report (Exhibit K) has reference to abscesses in the lung.

j) For animal No. 111 (a mid-level female) no grossly observable lesions are recorded in IBT's own records (Exhibits H and J) yet the final report (Exhibit K) has reference to congestion and abscesses in the lung as well as stomach ulcers. In addition to the mammary adenocarcinoma reported by the pathologist for this animal (Exhibit J) which we have signalled already is missing from the final report by IBT (Exhibits K and A) the final IBT report (Exhibit K) also fails to list other microscopic findings by the pathologist such as chronic respiratory disease, a grade 2 metritis and telangiectasis of the adrenal gland.

k) For animal 143 (a high-level male) internal IBT records (Exhibit H) list for gross changes grade 3 hemorrhage and grade 3 consolidation in the lungs and the mesenteric lymph nodes being swollen and hemorrhagic. The final IBT report (Exhibit K) lists only "hyperemia" for the lung.

m) The same problem of not reporting all gross lesions observed is present also for animal 25 (a control female): both adrenal glands hemorrhagic (grade 3), left one enlarged 3x, lungs hemorrhagic +2, cervical nodes hemorrhagic +3 - compare Exhibits H and K.

n) An apparently fictitious pneumonia is reported by IBT for animal 99 (a mid-level male) - Exhibit K - since Exhibit H makes no mention of such a lesion. The same is true with respect to stomach ulcers for animal 129 (a high-level male), for lung congestion and abscesses and stomach ulcers for animal 111 (a mid-level female), and pneumonia for animal 55 (a low-level male). For this last animal, the pathologist reports focal chronic nephritis (Exhibit J) but this is not reported by IBT (Exhibit K).

o) Gross changes observed (Exhibit H) but not reported by IBT

(Exhibit K) are also present for animal 113 (a mid-level female): hemorrhages grade 3 in the lungs, spleen reduced abnormally in size and hemorrhages in the stomach cardia - histopathologic changes in this animal are reported by IBT (Exhibit K) but there is no record of these (Exhibit J). We can thus sum up this section with the conclusion that a substantial number of tumors, suspected tumors and other gross and microscopic lesions were noted in these animals but not reported by IBT and that many lesions reported cannot be documented by any internal records IBT supplied for us.

Problems with the IBT contract pathologist.

Amongst these we can briefly mention the following:

a) IBT apparently had chosen not to report all findings made by Dr. Richter, their contract (Consulting) pathologist on this study. Examples of this are given in the previous sections of this communication. Additionally, we may mention here that Dr. Richter's report to IBT indicates NO (no optic nerve) for his examination of the eye and optic nerve in 24 instances, (Exhibit J) yet not a single one of these is reported by IBT (Exhibit K). Also evident in Exhibit J is the notation SI (section inadequate for examination) for the eye in 17 other instances and, again, not one of these was reported by IBT (Exhibit K).

b) It is amply evident that Dr. Richter did not perform in a manner expected of any professional pathologist who is called upon to render a judgment on what changes can be attributed to a drug product on test (see his conclusions in the introductory page

of Exhibit J). He apparently failed to satisfy himself that the information on identity of the animals on test and on gross changes seen in these animals as provided to him was reliable before he tackled the job of histopathologic "evaluation." Futhermore, the fact the "lesions described are those of spontaneous disease and they are not unusual for the rat" which is implied by him to be a justification for his previous statement, "There are no changes which can be attributed to the compound" - is totally unacceptable.

What this statement implies in an extremely misleading fashion is that unless one finds lesions which are either not seen "spontaneously" or usually for an experimental animal, the test agent cannot be blamed for anything. We would doubt that any chemical agent exists that elicits only "new" kinds of lesions not seen in any other circumstances. Unless one conducts a statistical analysis of the difference in incidence for <u>any</u> lesions between control and exposed groups of animals, no such judgment as rendered by Dr. Richter is appropriate. We have no evidence that Dr. Richter had in any way assured himself that he has a reliable basis of data to make such an analysis, that he is scientifically trained or compentent in making it, that he in fact made such an analysis or reviewed the results of anyone else who made it.

c) Dr. Richter apparently acted in a misleading manner in yet another way: by having reference only to those sections where he discovered microscopic changes (and not to those which he deemed negative for lesions) he is implying that all those sections without remarks are in fact negative. But it is extremely likely he did not examine a large number of these sections because Syntex indicates that it has no such sections. We have checked the list of such sections sent to us by Syntex (Exhibit M) for a number of animals in this study (all control animals and the high-level males for which many sections are listed by Syntex) and found the following sections missing:

Control-males	Animal No. 1	- parathyroid gland
	3	- spleen, pituitary gland and skeletal muscle
	9	- pituitary, thyroid and parathyroid gland, skeletal muscle and peripheral nerve
	11	- aorta, tongue, prostate, pituitary gland, skeletal muscle, peripheral nerve and spinal cord
	12	- parathyroid gland, skeletal muscle and peripheral nerve
	14	- aorta, pituitary gland, and skeletal muscle
	17	- peripheral nerve
	19	- aorta, tongue and parathyroid gland
(actually a female)	20	- uterus, parathyroid gland, eye and the tissue masses reported as tumorous in Exhibit A
Control-females	Animal No. 24	- spleen, urinary bladder, pituitary gland

25 - trachea, esophagus, pituitary, adrenal, thyroid and parathyroid glands

27 - either cecum or colon

28 - trachea and uterus

30 - esophagus, urinary bladder and skeletal muscle

32 - pituitary and parathyroid glands

33 - esophagus and parathyroid glands

34 - aorta, urinary bladder, uterus, parathyroid gland and skeletal muscle

35 - aorta, and parathyroid gland

36 - parathyroid gland

37 - aorta, trachea, and parathyroid glands

39 - aorta, esophagus, urinary bladder and pituitary gland

40 - tongue, pituitary and parathyroid glands

High-level males Animal No. 143 - either caecum or colon, pituitary and parathyroid glands

149 - trachea, either caecum or colon, eye, pituitary, thyroid and parathyroid glands

152 - esophagus, peripheral nerve and parathyroid gland

154 - trachea, spinal cord, pituitary, thyroid and parathyroid gland

These represent all animals with many tissues collected in these three groups on which Syntex reports having slides; there is among them not one which did not have one or more sections missing. Yet for none of these was there any indication by IBT (Exhibit K) that any section was not examined.

In a very few instances, Dr. Richter indicates in his report (Exhibit J) that some sections may not have been examined; we checked out the tissues for which he has such indications for only one such animal - No. 55 (a low-level male). Dr. Richter had checked as not having examined the trachea, lung, esophagus, eye and optic nerve, pituitary and adrenal glands (Exhibit J). None of these were reported as having been not examined in the IBT report (Exhibit K). Additionally, Exhibit M indicates that there were no sections for the stomach, small intestine, either cecum or colon, urinary bladder, prostate, seminal vesicle, skeletal muscle, peripheral nerve, spinal cord and skin; none of these are signalled as having been not examined by either Dr. Richter (Exhibit J) or IBT (Exhibit K).

Organ weights.

During the inspection we were told by Mr. Plank that the list of organ weights collected from the animals surviving the 22-months observation period (Exhibit E) was transcribed for input into the computer; this transcribed list is appended here as Exhibit F and the computer output is given here as Exhibit G.

Note that although weights for the pituitary gland are given in Exhibit E, these have been omitted from Exhibits F and G. It will be recalled from a previous section that many pituitary glands which were grossly enlarged or had tumors were not reported by IBT and this may be related to the omission of the weights for this organ from the final report (Exhibit A).

Interestingly, the final report (Exhibit A) contains information on the prostate (page 40) and uterus (page 41) but these do not appear in Exhibit G; they do appear, however in Exhibits E and F. The

reliability of the recorded weights of organs for the individual survivors is, at best, questionable. For example:

a) Animal No. 69 has recorded for it in Exhibit E a pituitary weight of 0.152 gms when most other weights are between 0.013 and 0.030 gms; thus this represents an increase some 5-10-fold which should have been picked up at necropsy. Exhibit H, however does not indicate an enlarged pituitary for this animal.

b) Animal No. 77 has an adrenal gland weighing 0.203 and the adrenal weight of the animal just preceding it in Exhibit E (No. 75) is only 0.018 gms - a difference more than 10-fold. Now either one of these is abnormally small or one is abnormally large but Exhibit H has no reference to either adrenal gland being of abnormal size. The same problem is present also with animal No. 152.

c) Extreme weights for the liver are noted for animals No. 19 (27.56 gms) and 107 (9.30 gms), again with no accompanying notes of any kind for the liver size in the post-mortem observations list (Exhibit H).

8/10/76

Manfred M. Hein 8/10/76

NDA 17-581 MEMORANDUM OF MEETING

August 20, 1976

Present from Syntex:

Harold C. Anderson, M.D., Medical Director,
Corporate Regulatory Affairs

Stuart Bessler, Ph.D., Director
Department of Biostatistics

Anthony A. Bourdakis, Director of Compliance
and Development, Corporate Regulatory Affairs

Albert Bowers, Ph.D., President
Syntex Corporation

Kenneth Carter, M.D., Vice President
Corporate Regulatory Affairs

Kenneth Dumas, M.D., Senior Vice President
Director, Institute of Clinical Medicine

John Fried, Ph.D., President
Syntex Research

Robert Hill, Ph.D., Assistant Director
Institute of Clinical Medicine

James D. Mutch, Associate Director
Regulatory Affairs

Eugene J. Segre, M.D., Vice President
Clinical Investigation

Virgil Thompson, Esq., Associate Director
Law Department

Alan Kaplan, Esq., Counsel
Kleinfeld, Kaplan and Becker

Robert Becker, Esq., Counsel
Kleinfeld, Kaplan and Becker

Present from FDA:

Carl M. Leventhal, M.D., Deputy Director/BD

Marion J. Finkel, M.D., Associate Director
for New Drug Evaluation/BD

William D'Aguanno, Ph.D., Assistant Associate Director for NDE (Pharmacology & Toxicology)

William Gyarfas, M.D., Director, Division of Oncology & Radiopharmaceutical Drug Products

David Richman, Ph.D., Supervisory Pharmacologist, HFD-150

Adrian Gross, DVM, HFD-108

Frances O. Kelsey, M.D., Director, Scientific Investigations Staff

Mr. Arthur Levine, General Counsel

Albert Norris, M.D., Medical Officer, HFD-150

Mr. Daniel Hillstrom (HFD-340) Observer

Mr. Jerome A. Halperin, Deputy Associate Director for NDE (Scientific)

→ Mr. Ronald H. Britten, HFD-108

Subject: Naproxen, NDA 17-581.

The visitors came at their request to present their reanalysis of the 22-month rat study performed by Industrial Bio-Test. Three volumes of data were left with the FDA. The introduction was made by Dr. Bowers in which he indicated that the detailed report had been prepared by Syntex. Syntex had obtained considerably more information than had FDA on its inspection and such information included hand-written notes which were not available at the time of FDA's inspection. The next speaker was Dr. Dumas, who stated that considerable work had been performed by Syntex to reconstruct the report. Syntex feels strongly that the data are totally useful to support safety and the findings are consonant with those seen from shorter animal studies done elsewhere. Dr. Dumas stated that with respect to body weights of the animals, the errors in the Industrial Bio-Test report were mostly recording errors.

Dr. Bessler continued with a statement that the lack of raw data on body weights for certain periods of the study was not important because the study was a chronic study. Dr. Bessler explained in great detail how the errors came about in the weights which were recorded, and how these weights could, in the majority of cases, be logically transposed to the appropriate animals. He stated that there were a few weights which could not be accounted

for but that they did not invalidate the study. Dr. Bessler also stated that organ/body weight ratios and urinalyses data as calculated by Syntex were not significantly different from the data found by Industrial Bio-Test.

Dr. Hill then discussed the gross and histologic findings. He stated that the raw data on these findings were obtained from IBT and examined by Syntex. A few histopathologic observations noted by IBT's pathologist were not included in the report but they were of such a nature that they would not materially affect the conclusions.

Dr. Dumas went on to discuss the tumor findings. He stated that 107 animals had completed 16 months or more and that 87 animals had completed 18 months or more. This number of animals, he felt, was adequate to observe for tumor incidence. He stated that even in the presence of autolysis gross observations are valuable in searching for tumors.

Dr. Dumas concluded his presentation by stating that Syntex felt that the 22 month study was adequate to demonstrate safety of the compound and, taken in conjunction with the other animal studies and the fact that large numbers of patients had received naproxyn for up to three years and some as long as six years, there was enough evidence of safety to continue marketing of the compound.

Notwithstanding this conclusion, Dr. Bowers had stated earlier in the meeting that the firm intends to perform a new rodent study using 800 animals (presumably, 100 animals per sex per dose level times four dose levels, including controls).

There was some discussion on the part of FDA with respect to the data presented by Syntex and expressions of concern that Syntex had not monitored the 22 month rat study at any time during its course.

The visitors were informed that we would review the data carefully and the meeting was brought to an end.

M.J.F.

Marion J. Finkel, M.D.

cc:
Orig. NDA 17-581
FDA Attendees, HFD-150/Mr. Hein
HFD-150, HFD-1, HFD-30/Ms. Mansur
MJFinkel:eks 8/24/76/8/31/76

MEMORANDUM

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

TO : Frances O. Kelsey, Ph.D., M.D.
Director, Scientific Investigations Staff
HFD-108

DATE: August 30, 1976

FROM : M. Adrian Gross
Scientific Investigations Staff, HFD-108

SUBJECT: NDA 17-581, Syntex - Naprosyn: Adequacy of the 22-months rat study carried out by Industrial Biotest (IBT)

Dr. Finkel asked that I comment on the latest Syntex supplement to this NDA dated August 18, 1976, and on their oral presentation made two days later.

The main object and thrust of the statements by Syntex is that the IBT study, for all its shortcomings, can be regarded as being of an acceptable quality and as indicating no hazards associable with the agent on test.

After reviewing their rather massive written supplement to the NDA and listening to their oral statements, I have concluded that no cogent or persuasive argument has been presented to deter us from our view that this IBT study is totally unacceptable.

The recent Syntex effort consists mainly of two parts:

a) an attempt to assure us that the extensive problem with the identity of animals on test is in reality nothing more than animals being mistakenly assigned the identity of their adjacent cage neighbors during weekly weighings; Syntex believes that such observations can be meaningfully "realigned" and they also believe that no inter-group mixups of animals had taken place; they state they can do this for all but a handful of animals on test.

b) taking this new version of the IBT-generated data which Syntex now views as being "reconciled", they embarked on a massive statistical analysis of it whose object is to demonstrate that the original conclusions on the safety of this drug product are justified.

The first of these (the attempted reconciliation of the internal inconsistencies of the data) strikes me as a rather odd exercise to be undertaken by Syntex who has no first-hand knowledge of the details or the manner in which this study was carried out. They certainly presented to us no indication that any responsible or knowledgeable individual at IBT subscribes to or agrees with this tangled set of conjectures and speculations which are being presented by Syntex as indisputable facts. I cannot see how, unless Syntex is endowed with remarkable clairvoyance, they can make such statements as "the eleven weights for animal 57 collected between 2/4/71 and 5/24/71 are in fact the weights of animal 58. Animal 57 was necropsied on 9/29/70," (page 17 of the Syntex supplement). While I would agree that this could be a plausible explanation - we do not really believe in animals coming back to life after death - it is no more than that and certainly not "a fact" positively known to Syntex or even to IBT at this point in time.

Some of these "realignments" are not necessarily confined to adjacent animal numbers but they demand rather so fanciful an imagination as to make their likelihood questionable in the extreme. For example, let us consider some of these merely from one of the eight treatment groups, the high-level females:

a) The weight of animal No. 149 shown by IBT in their records to be 640 gms and to have been collected on 1/21/71 is now deemed by Syntex to belong not to a rat with an adjacent number but rather to animal No. 152 for which the weight of 385 gms is recorded by IBT on that day. But this latter weight is said by Syntex to really belong to animal No. 157 (5 numbers removed from 152) whose next recorded weight was 405 gms.

b) A weight of 540 gms said by IBT to have been collected on 9/28/70 for animal No. 151 is said by Syntex to really belong to animal No. 152. Since the latter is recorded by IBT on that day to have been 255 gms., Syntex said this weight (255 gms) really belongs to animal No. 153 whose immediate "before" and "after" weights are being recorded by IBT as 305 gms.

c) For animal No. 145 the entries of 14 body weights are missing from the IBT records. Syntex now says that these can be found in the 9 weights of animal No. 144, 1 weight of animal No. 143 and 3 weights of animal No. 142 (one missing weight from the record for animal No. 145 cannot be "reconciled" by Syntex). If this entire scenario is true, the following sequence of weights in grams for animal No. 145 would follow: ...322, 297 (eight days later), 331 (six days later), 395, 365, 375, 370, 340, 368, 372, 365, 370, 390, 350 (nine days later), 415 (eight days later), 410, 420, 435 and 365 (eleven days later). Interspersed amongst these weights are gaps up to nearly three months in duration when the animals were supposed to have been weighed weekly. That the latter was almost certainly not done is indicated also by the peculiar spacing: eight, six, nine, eleven days between successive weighings.

These Syntex "realignments" or "reconciliations" of the body weight data, even if taken at face value, do not even begin to "explain" all the odd and extreme variations in the body weights ascribed to these animals. A few examples of these (on which Syntex is silent) is taken from merely the control group:

	Date	Weight in Grams
Animal 12	04/21/71	863
	04/27/71	773
	05/15/71	825
	05/24/71	740
Animal 16	06/08/71	670
	06/23/71	605
	06/30/71	535
Animal 21	05/15/71	365
	05/24/71	280
	06/01/71	320
Animal 20	02/16/71	690
	03/10/71	544
Animal 19	04/21/71	635
	04/27/71	583
	05/15/71	640
	08/09/71	670
	09/15/71	425
Animal 18	04/21/71	763
	04/27/71	680
	05/15/71	730
Animal 14	04/21/71	647
	04/27/71	590
	05/15/71	620
	06/08/71	635
	06/23/71	560
	06/30/71	575
	07/16/71	625
Animal 13	10/05/70	528
	10/12/70	450
	10/20/70	538

	Date	Weight in Grams
Animal 12	02/16/71	852
	3/10/71	756
	3/18/71	771
	4/5/71	812
	4/27/71	773
	5/15/71	825
	5/24/71	740
	06/01/71	730
	06/08/71	800
Animal 10	10/20/70	702
	10/26/70	678
	01/21/71	714
	02/04/71	600
	02/11/71	522
	02/16/71	490
Animal 7	06/30/71	800
	07/27/71	520
Animal 6	05/15/71	805
	05/24/71	750
	06/01/71	790
	07/16/71	715
	08/09/71	615

Because of this kind of variation, not addressed to by Syntex in their "realignment" operations, I prefer to believe that the explanation for this must lie elsewhere: the most plausible reason would be that, contrary to statements made by Syntex, animals from entirely different groups were likely mixed-up in this study.

Even if this were not true and all mix-ups were indeed confined to "within" treatment groups (as Syntex alleged though it cannot be positive on this) this would still be an unacceptable experiment. Why? The basic purpose of an experimental animal trial is not to determine at the end that the proportion of adverse reactions in exposed groups is not significantly increased over that in the control group. Rather, it is to predict, where possible, the kind of adverse reactions likely to manifest themselves in the most susceptible humans exposed to the drug. If it were not for this fundamental purpose, we would not require at least one exposure level to be several times that proposed for humans.

If now the agent on test were to affect only part of the individual animals or humans exposed (the more susceptible segment in the entire population) in a persistent (non-reversible or actually progressive) manner, should this not be known by repeated observations over some time-frame of the affected individuals? But how can repeated observations have any meaning if the identity of the animals on test is in doubt? Suppose a certain test group of animals turns up with the same number of tumors at the end of two years as an equivalent control group; suppose also that most of the tumors in the exposed group occurred six months or so before those in the control group and that this difference is sufficiently significant to class the agent on test as a carcinogen. But how is one to determine this in a study of this sort where the sponsor cannot reliably assure us which animal is which?

How can one correlate anatomic pathologic changes observed post-mortem with the ante-mortem observations if the identity of the animals is in doubt? Is this not important when one is trying to correlate, say, urinary system changes noted either by gross of histopathologic examination of tissues with periodic urinalysis determinations?

More important with a drug agent such as Naprosyn which is known to cause gastro-intestinal ulcers, is it not appropriate to know at what time signs referrable to this (such as inappetence, enteritis, emaciation, anemia, etc.) first become manifest or how persistent they are? But how is any of this to be determined if one cannot positively identify any animal on test?

It is largely for this sort of reason that we ought to dismiss Syntex' argument that as long as we have no positive evidence of intra-group mix-ups of animals this toxicologic study is adequate.

There are other problems with the identity of these animals brought out in our EIR (and in the letter sent to Syntex by Dr. Crout) which are entirely ignored by Syntex in this latest submission. Items:

1) the many animals which are said to have died several times, often with entirely different findings,

2) the conflicting and inconsistent dates of death or times to death reported by IBT,

3) the fact that certain lesions such as tumors are recorded as having been observed for some animals at some time but for different animals at the next observation period,

4) the extreme variability amongst weights of all animals in a certain groups at any given time.

Because of all this, I would conclude that the matter of the identity of these animals is far from having been satisfactorily resolved by Syntex at this time.

This would tend to invalidate most if not all the elaborate statistical analysis carried out by Syntex since if we have no good assurance that all animals were indeed what they were represented to us as being, any statistical analysis based on data of this sort assumes a questionable or useless status.

But this is not the worst we can say about the conduct of this particular study; no attempt whatsoever was made by Syntex to deal effectively with the following issues:

a) the fact that approximately 60% of the animals dying in this study (and there were only 43 or 44 survivors out of the total of 160 animals) were noted by IBT to have been TBD/TDA or TBD/NTT (meaning too badly decomposed; technician destroyed animal or no tissues taken). This indicates not only a callous disregard for the adequacy of gross and histopathologic examination of the tissues, perhaps the single most important feature of any long-term experimental toxicity trial, but also that the professional pathologist was likely not present at the time of necropsy. If so how can one vouch for the adequacy of the tissue samples collected for histopathologic examination? More important, how can one explain results of such examinations for those animals for which tissues are noted in IBT records <u>not</u> to have been collected?

Furthermore, how can one defend the adequacy of such gross observations reported to FDA as "pneumonia" or "lung congestion" and many others for the animals noted to be "too badly decomposed"?

b) The many instances of tumors or suspected tumors on which we found entries in internal IBT records yet which were not reported to the FDA and many of which are still not reported even now by Syntex.

c) The large number of cases where pathologic changes other than tumors were either incompletely or incorrectly reported to the FDA or not reported at all.

d) The fact that extreme values for certain organ weights are not consistent with the gross observations collected at necropsy - another indication of poor supervision of the technicians doing this work and/or their questionable competence.

e) The fact that many tissues implied to us as having been examined microscopically were in fact not even prepared for such examination.

f) The questionable interpretations made by the pathologist chiefly responsible for this study.

g) The fact that IBT records on dates of death or times to death for experimental animals are internally inconsistent or inconsistent with other records found at IBT.

h) The many "missing" records on this study which make it questionable that some of these procedures were in fact carried out:

1. Systematic records of ante-mortem observations.
2. Most of the gross post-mortem examination records.
3. Any records of hematology operations.
4. Any records of clinical chemistry determinations.
5. Any records of the terminal (22 months) urinalysis determination.

i) The improper way in which animals were sampled for urinalysis determinations.

In conclusion, it seems amply evident that not only has Syntex failed to convince us this was an acceptable study, but at this stage I cannot see how anything of value can be retrieved from it even at the price of doing extensive additional work such as statistical analysis or repeat histopathologic observations on existing or additional tissue.

The basic problems on the identity of the experimental animals and on the integrity of gross observations or of the tissue samples collected for microscopic examination cannot, in my view, be solved at this time. If this is an acceptable fact, no extra work no matter how extensive can meaningfully retrieve anything of value from this work.

Finally, there is the matter of the tumors elicited in the animals on this study. Syntex, in their latest submission, present on page 196 a new version of the tumors observed in this study which is different from what was presented originally in the NDA (pp. 58-59 of the IBT report).

We can note that even this new version does not report all tumors actually noted in this study - as an example, female animal No. 111 (a mid-dose female) is reported by IBT to have had a mammary adenocarcinoma in the detailed table of individual animal findings, but this is not reported by Syntex in their latest submission.

If we limit our attention to merely the mammary tumors that Syntex acknowledges in this supplement and add to this list the adenocarcinoma for animal 111, we now have 1/20 control females, 4/20 low-level females and 4/20 mid-level females with mammary tumors. The contrast between 1/20 positive control animals and 8/40 (a four-fold increase) positive test animals is significant at p=0.12 which is of appreciable degree. If now we say that because of the questionable identity of the animals and the manifestly unsatisfactory manner the pathology operations were carried out we would have confidence that only 22 of the 32 females in the low and middle level were truly negative for mammary tumors, a new contrast of 1/20 positive controls versus 8/30 positive test animals (i.e. a 5.33 fold increase) would be significant at the 0.05 probability level.

All this suggests to me that a not insignificant hazard of mammary neoplasia possibly due to this agent has been elicited in this study.

RECOMMENDATIONS

1. We continue to regard this study as of an unacceptable quality.

2. We take note of the hazard of mammary neoplasia uncovered by this study and relate that to information of such action by other similar agents - see Mr. Hein of HFD-150.

3. This entire matter be submitted to the Associate Director of Compliance of the Bureau of Drugs with a view to determine whether IBT should be charged with withholding the pertinent information on the conduct of this study (with or without the knowledge of Syntex) which would have had an effect on a regulatory decision and of submitting or causing the submission of false information to the government.

4. That a parallel procedure be undertaken in the Bureau of Drugs to compel IBT to show cause why any of its work submitted to IND files or NDA's be continued to be regarded as satisfactory.

M. Adrian Gross

AUG 30 1976

PHARMACOLOGY REVIEW OF IND 5281 AND NDA 17-581

Pharmacology review of an evaluation of the raw data by Syntex involving the 22 months rat study carried out at Industrial Biotest Laboratories (IBT) and identified by IBT as B 7922 and by Syntex as R 53540.

NAME OF DRUG: Naproxen (Naprosyn)

NAME OF THE SPONSOR: Syntex Laboratories

RELATED IND: 5281 RELATED NDA: 17-581

INTRODUCTORY NOTES:

1) Syntex commissioned IBT to carry out an 18 month rat toxicity study (which was later extended to 22 months). Study duration was November 25, 1969 to September 17, 1971. A report to Syntex as made by IBT about November 1971 but returned for modification. A resubmission on January 4, 1972 was accepted by Syntex and subsequently submitted in support of IND 5281 under cover letter of March 22, 1972. It was also submitted to the NDA.

2) An on-site investigation by Inspector D. Stelter of the Waukegan Residence Post, Dr. Adrian Gross of HFD-108 and Manfred M. Hein of HFD-150 was made June 21-24, 1976 to compare the raw data with that in the IND submission. Inconsistencies with respect to tumors between two parts of the report led to this effort. The bulk of the available data was copied and later evaluated at Rockville by Gross and Hein. Their observations are given in the Memorandum of August 10, 1976 appended to the EIR report.

3) An in-house FDA meeting July 6, 1976 initially suggested the need to possibly withdraw the NDA for Naproxen because there was thought to be a lack of an adequate long-term toxicity study. (See memorandum of July 6, 1976 meeting and memorandum of July 20, 1976 from Dr. Kelsey of HFD-108 to Assistant Director for New Drug Evaluation).

4) Syntex was alerted by letter of August 5, 1976 (and possibly also by phone) of our intention to ask that Naproxen be withdrawn from the market through formal procedures.

5) A meeting was held between FDA, (principally Dr. Gross, Mr. R. Britten and Mr. Hein) and Dr. Hill and an associate of his from Syntex August 11, 1976 to discuss the August 5, 1976 letter and to compare the Syntex inventory of raw data from IBT and Syntex with that of FDA. Syntex also received an overview of our findings leading to issuance of the letter.

6) Syntex met with various components of FDA on August 20, 1976 and verbally presented a 'reconstruction' of the IBT data into a more carefully analysed and evaluated report. This was also submitted to the NDA as two volumes and forms the basis of this review.

7) The basic raw data available to Syntex from IBT is the same as that in the hands of FDA.

Some of the data relating to food utilization, diet formulation and urinalysis was examined June 24, 1976, but not copied at that time by FDA as it did not help in relating to the identification problem of specific animals. Some of this data also available to Syntex was subsequently recovered also by D. Stelter at IBT and copied.

Certain important raw data is apparently irretrievably lost (it may not have ever existed) and is not available to either FDA or Syntex. The later includes the hematology data, certain weight recording sheets and the forms used at time of autopsy.

8) It is Syntex's contention that the "reconstructed data" can be used as a valid long term toxicity study. The primary aims of such study should be an administration of a test substance at elevated dose (in relation to clinical use) for a major portion of the animal's life in an adequate sample of animals to measure any insults that the agent may exert over long term administration and suggest that a low carcinogenicity potential exists which would obviate the need for additional specialized long term carcinogenicity studies. Syntex will readily admit to many of the shortcomings of the data, i.e., lack of identifications of technicians and responsible supervisors, some inconsistencies that cannot be explained 5-6 years after the end of the study, that original study report had shortcomings in analysis of data and that an unusually high number of autolysed animals was present.

This initial review of the 'reconstructed' data is based on the August 20, 1976 submission without any attempt to reconcile the computer-generated data tables and other report findings with the raw data at this time. (We assume that Syntex verified the computer outputs with the raw data for accurate keypunch operation, programming, etc., but have no assurance of this at this time.). The report is in sections with appendices, and the comments below relate to the same identification system.

A) Introduction - This poses the question of whether the reconstructed study is valid. Syntex concludes that the findings are similar to findings in other studies with this drug carried out by them and others, albeit for shorter periods of time. The high mortality rate in the later stages of the study is said to be expected. We would tend to disagree with the last point. An examination of other long-term toxicity studies with comparable (pharmacologic activity) drugs will show a high mortality rate in the later stages of the study, but not to the degree seen in this data.

Syntex attempts to divide the rat population into three classes:

1) Animals with a full spectrum of data,

2) Animals with less than full data, but still data with adequate information for analysis,

3) A small number of rats (8/160) which cannot be evaluated.

In the finding of inadequate and incomplete weight records, a lack of periodic physical examination records ante mortem over much of the study (and when present of dubious quality), the lack of opthalmological records the lack of hematology data, a lack of individual urinalysis records, an autolysis rate of about 56% of the rats (and thus at best a biased pathological examination) deletions from the necropsy log (and dual entries) and lack of agreement between the necropsy log, the histopath form prepared at autopsy (when available), the study report and the pathological report in a sizeable number of cases, it must be concluded that there is no complete spectrum of data for any rat in accordance with the protocol agreed upon between the IBT and Syntex. It is also noted that the survival rate, especially after about 15 to 18 months is so low especially at high dose that the observations have only dubious statistical analysis value. We find a careful following of the protocol (included in the original NDA submission) with Good Laboratory Practices would have resulted in a satisfactory study by IBT.

B) Animal Identity Resolution - Syntex analyzed the body weight records after passing them into and out of the computer and suggests that animals not recorded as weighed just were not available for weighing. One must presume that they were dead, but perhaps they were not. Entries of weight data subsequent to many of the missing entries were analysed and were attributed to another rat. It was claimed that this "invariably" was in relation to adjacent cages (or animal numbers).

Table B1 and B9 (Control males): A shift on May 15, 1971 of animal #12 weight to #13 (then dead) and in entries of February 4, 1971 through June 8, 1971 for animal #16 in the #15 space may have occurred. The entries for June 1, 1971 through July 16, 1971 in the #20 rat space are likely those of #21. This however does not explain the 840 g recorded on February 4, 1971 for rat #4.

Table B2 and B10 (Control females). The values for animal #21 June 1, 1971 through July 16, 1971 are under rat #20 probably, but we are assured that each treatment group was kept separate and this presumably included separation of sex within each group. Here two shifts are likely (entry of 413 g under #31 and 450 g twice under #29). However the 413 g entry does not favorably compare with a 440g 8 days previously and 430g 8 days later. There also is no explanation for the absence of a value for #30 on May 24, 1971.

Table B3 and B11 (Low dose males; T-1) The slippage of #45 to #44 and back again to #45 on or about May 15, 1971 may be a simple recording error. The shift of values of #58 to #57 February 4, 1971 through May 24, 1971 and then back to #58 may have occurred but does not explain the absence of a May 24, 1971 value for rat #59. We suspect a further mixup as #59 on May 15, 1971 weighed 825g and on June 1, 1971 only 745g. The #44-#45 shift may also be questioned as May 15, 1971 weight was 545g and May 24, 1971 weight 445g.

Table B4 and B12 (Low dose females; T-1) On May 15, 1971 the 355g entry under #72 is suggested as belonging to #73 and May 15, 1971 and May 24, 1971 values under #76 to #77. This does not explain the May 15 and June 8, 1971 entries under #71. The 383g under #71 may be the missing value for #73 and the 550g value on May 15, 1971 that of #69 but this is unlikely as 685 and 690g are recorded 18 days pre and 9 days post this value. Note also here suspected mixups with cages other than "invariably" adjacent cages.

Tables B5 and B13 (Mid dose males; T-2). The May 24, 1971 entry of 745g for #84 is suggested as that of #86; the May 24, 1971 value of 605g under #82 as that of #81 and entries of June 23, 1971 of 660g and July 16, 1971 of 643g under #82 as that of #83. A February 4, 1971 weight of 840g under #88 is attributed to #89 as it seems to Syntex to be a more appropriate value then the 710g value originally listed. The absence of any weight value for May 24, 1971 under #85 is unexplained.

Tables B6 and B14 (Mid dose females; T-2). The 490g weight of rat #117 is attributed to #116 on August 9, 1971. The 290g value under rat #113 on May 24, 1971 is suggested as that of #116. This seems unlikely to this reviewer as the May 15, 1971 weight for #116 was 450g and the June 1, 1971 weight 485g. Weight values on April 27, 1971, July 16, 1971, July 27, 1971 and August 9, 1971 under #111 and May 15, 1971, May 24, 1971, June 8, 1971 and June 30, 1971 under #109 are suggested as part of record for rat #110 in the 'reconstruction'. A 325g weight May 24, 1971 however is unlikely as on May 15, 1971 rat #110 weighed 475g and on June 1, 1971 540g in this scheme. The April 27, 1971 weight for animal #120 is still missing and unexplained.

Table B7 and B14 (High dose males; T-3). April 27, 1971 and May 24, 1971 values of 655g and 340g respectively are attributed to rat #122 instead of #121. We concede this may be the case for the 655g weight but cannot be accepted for the 340g on May 24, 1971. The latter could fit possibly #145 (a female) but not #122 where prior and post weights are 645 and 650g.

Tables B8 and B15 (High dose females; T-3). The October 20, 1970 absent value of #141 is unexplained. Missing value for September 28, 1970 for #153 is said to be the entry under #151. A 540g on this date with prior and post values of 305g and 305g respectively suggests that this is most unlikely. Values for #145 after January 21, 1971 are variously attributed to entries under rats #142, #143 and #144 as well as four values under #145. An analysis of the weights suggests that this may not be the correct reconstruction. A 640g value under #149 for January 21, 1971 is attributed

to #152 and weight recorded there (385g) is suggested as that of #157. These are hardly adjacent cage changes. A 580g value April 27, 1971 is attributed to #152 However, prior and post values of 653 and 605g are not supportive of this.

We have also "eyeballed" the revised tabulations of weights generated by Syntex and note the numerous instances where a weight is not fully in agreement with that of prior and post observed weights and also considered the time interval between the specific weight recordings. Some of these aberrant or nonconforming weights are less than extreme, others deserve questioning as they represent further evidence of mixups or faulty recording on raw data sheets (i.e., adding or subtracting 100 or 200 to the recorded weight). Also the weight recording system may not be in calibration. In this regards we call attention to the following rats from the control group where drug effects can thus be excluded.

Rat #	Dates
5	July 16, 1971
6	May 24, 1971
7	July 16, 1971 and July 27, 1971
8	May 24, 1971, June 1, 1971, June 8, 1971
10	October 26, 1971
12	May 15, 1971
14	April 27, 1971
18	April 27, 1971
19	April 27, 1971 and September 15, 1971
13	October 12, 1971

(In this group of control males attention is also directed to the rapid decline in body weights of #5, #6, #7, #12, #17 and #20 preterminally. We surmise this to be a reflection of either disease or possibly poor animal husbandry (i.e., lack of feed or water). In the group of control females attention is directed to weights not in agreement with prior and/or post observed values in the following:

Rat #	Dates
21	May 24, 1971
22	April 5, 1971, April 13, 1971, May 15, 1971
27	May 15, 1971, July 27, 1971
28	April 5, 1971, June 1, 1971
34	June 8, 1971

The extreme variation between rats in the same treatment group (i.e., all control males or females) is noted. Some of the female rats tend to weigh the same as those of the usually heavier male group (note #39, #35 and #25) and others less than half of this at comparable points in the study.

Syntex has recalculated the group means. Tables B17-24 give the realigned values, but they fail to concede many of the nonconforming values and included them in their analysis of the means for different groups at various times.

Syntex in their analysis of data has excluded #87, 102, 119 and 131 from weight and other analysis as there were conflicting dates of death in different records. For rats #4, 53, 55 and 76 weights were recorded after supposed death according to reconstructed weight data and the necropsy log and other evidence. These were also excluded from further consideration.

Table B25 lists animals as to the presence of gross/histo/autolysis on necropsy for comparison with the entries in the summary and whether animals survived after 18 months. Intent seems to be that a sizeable number of treated animals survived 18 months and so this can be used as a cancer screen study. In the rat a proper carcinogenic study should be carried out over 24 months. Syntex tries to convince us that gross autopsy was possible and indeed done in almost all autolysed animals. Our own FDA investigation suggested that 58% of the animals dying before term were in some state of autolysis and largely thrown out by the caretakers before an autopsy could be effected. (The TBD/TDA group - "too badly decomposed/technician destroyed animal" group and the TBD/NTT group "too badly decomposed/no tissues taken"). Some of these animals appear however in the summary (prepared by J. Plank) and contain entries for gross and histological data. To the credit of Syntex no histology was considered on any autolysed animals even though some entries are in the Plank summary. Overall 68/160 rats were autolysed to some degree. This is 68 out of 117 that died sometime prior to end of the study.

C) Drug Administration - Examplatory calculations of dosing are given and raw data sheets from IBT support that this was done but we have no evidence that the food-drug mixture could meet by assay the intended formulation. IBT assays of other drug-food mixtures using the same mixing methodology are said to be by IBT homogeneous. Syntex suggests that the toxicity differences between the groups may be considered as evidence that different doses were actually administered to the rats. The large variation in the weight of specific animals within a treatment group however suggests that not all animals in each group got the same intended drug dosage. It is possible that the drug-food mixture induced a taste aversion by some rats (they did not eat) a fact that needs to be established in each drug feeding study before engaging in as large a trial as this one. Lack of feeding due to absence of drinking water or absence of available food cannot retrospectively be proven one way or another at this time.

D) Body Weights - Syntex admits to the absence of any weight data for the initial 8 weeks but does not consider this as critical. The mortality was small during this time. Without this data we cannot determine if all the animals placed on test in any treatment or control group had some sense of homogenity when placed on test. If not, this could explain the large intra-group weight differences mentioned before. Despite provision in the protocol, weighings of animals were done less frequent than once a week unless there were selective "losses" of certain raw data sheets. This is also discounted by Syntex as an important shortcoming of the study. (With full weekly records of weights the "Reconstruction" could be more believable and single nonconforming weights more readily discounted as

clerical errors). Syntex like FDA also noticed use by IBT of 8 and 9 week weight summary data for the 10th and eleventh weeks and errors in computation and record transfer.

The 'reconstructed data' was subjected to analysis and Syntex compared recomputed IBT data (Syn/IBT) with the mean 'reconstructed' data (Syn) and IBT data as reported. (Tables D1 and D2). Note now that Syntex is using all the data available rather than being satisfied with the data points selected by IBT. ("Monthly values after week 12"). The actual means recorded are largely not significantly different in most cases. However, as means are composites of many individual values any significant changes up or down are not likely. The larger shifts at the end of the experiment especially in the T2 and T3 groups are a reflection of the few animals left in the study and their possibly unhealthy state. In no case has there been any attempt to compute a standard error for each mean. Syntex in tables D 3-5 further selected out data to just 7 weight collection data points. Notably here the May 15, 1971 weights are used that represent the data on which extensive "reconstruction" was done. The choice of the dates selected represents data points at 1.9, 11.1, 15.8, 17.7, 18.3, 20.1 and 21.7 months of study. It would appear that these dates chosen are in a logarithmic progression and not equally representative for all phases of the study as a selection of data points at 3, 6, 9, 12, 15, 18, and 21 months would do. Significance is claimed for male subgroups on May 15, 1971 and July 21, 1971 using a linear contrast test. Former date has been discussed and latter is near the end of the study when some rats were in a state of rapid weight loss and fewer rats/treatment group were available for study.

E) Organ Weights - Syntex had handwritten records from IBT (p. 153, 154 and 155 of appendix III) which included pituitary gland. The second set prepared for the keypunch operator at IBT (p. 156-161) and the IBT computer printout (available to FDA) does not contain the pituitary. Syntex re-entered the data in their computer system so as to be able to also generate tissue to brain ratios. This data is of course limited to animals sacrificed at the end of the experiment. Any intergroup analysis is biased by 4 male tissue sets in T1, and three in T2 versus 13 sets for females of group T1 and 7 female sets in T2. Control group had 6 males and 10 female entries. The T3 group was omitted as having too few tissues.

Syntex in their analysis, like IBT, drop the pituitary even though they had the data. Group differences in the pituitary are likely whereas not seen in other tissues. We otherwise concur in the Syntex evaluation of this parameter.

F) Pathology Summary - It is my understanding that the Pathology and Histology will also be discussed in detail by Dr. Gross of HFD-108.

As far as I can recollect we were given to understand during our IBT inspection that at the time of this study (1970/1) one of the technicians doing necropsies was Marylou _____. On questioning we determined that she is also the one that prepared the necropsy log and transcribed

the data from the necropsy sheets (also identified as a printed Histo/Path report form of which about 30 were found. These were prepared only on animals dying prior to study termination). Thus the designation TBA/TDA (includes the NTT cases) must be accepted as correct and supercede all other data information. If the animal was destroyed by the technician no autopsy record was made and no histology slides were prepared. Thus the 68 so designated rats were not examined and any findings in the summary and elsewhere are unexplained.

Syntex maintains that the CVs of technicians are in Appendix Section VIII. We fail to see one for Marylou_____.

Except for certain drug induced GI pathology Syntex claims that findings are incidential and that the tumors are satisfactorily explained in a special section 'M'. Histological exams were done largely by Dr. Richter and in a few animals by Dr. D. Gordon (see Appendix Section V). This reviewer does not recall seeing some parts of the Gordon reports (there are really two, with one just covering GI tissues and generated after submission of the study to IBT in January 1972) and also the Richter report bears verification with our data set as it may contain some additional entries. We should determine if there were any changes in this raw data since June 1976 by IBT or Syntex, and if so by whom. The pathology reports generated by Gordon and not seen previously by this reviewer do not materially change the evaluation made and dated August 10, 1976. 14 of the examinations by Gordon are of the GI tract only and made February 1, 1972 (after IBT report submission and acceptance by Syntex). Two entry records (for rat #113 and 102 (102a or 102b? or?) are part of both of Gordon's reports.

G. Gross Pathology - Gross Pathology (Necropsy) is claimed here for 144/152 rats with satisfactory results. In view of discussion above of 68 rats with TBD/TDA status this is to be questioned. Chronic respiratory disease was reported as most common finding consisting of either pneumonia and/or consolidation, congestion, hyperremia or hemorrhage of lungs. 115/152 animales in this group have this designation in table G2. This finding is especially hard to make in autolysed animals even if a necropsy was done as claimed. It should be noted that in cases where there was an autopsy sheet prepared and the animal was in TBD/TDA status no notation is found in lung to indicate pathology or in the necropsy log. The 30 necropsy report forms (out of the 116 rats that expired prior to termination of study) were not part of the Syntex submission. The FDA review team checked these and notations thereon were faithfully transcribed to the necropsy log.

Pituitary enlargements, so called adenomas are said to be more frequent in controls, but the organ weight table in appendix V does not support this contention. (It is admitted that the data bases are not identical in all respects as one group is limited to 22 month sacrifices and the other covers data from deaths occurring before this date also).

Syntex suggests that there are no significant tissue pathology differences between control and treated rats but in our view the reliability of the data base is so questionable that even this statement must be questioned. If the histological findings are also considered and if some ante mortem observations (by animal caretakers) and biochemical determination data were available—assuming that correct animal identification existed—some limited analysis on non-autolysed animals may have value.

A larger instance of GI ulcerations and hemorrhage was to be expected from this drug. (This type of agent is also often an agent that affects blood coagulation besides having anti-inflammatory properties). The reported findings however suggest that the doses used (2, 10, 30 mg/kg) were not high enough for this to be the cause of death in most cases and even higher doses may be tolerated by some rats. The G2 table certainly supports the view that the agent has effects on bleeding (see entries for stomach, GI and heart). It causes increased liver pathology and at high dose causes increased lymph node enlargement (a response to increased infection rates? reduced resistance to infection?).

The listing of pituitary adenomas solely on gross observation and without histological verification is unwarranted.

H) Gross Pathology Exception Report - Syntex tries to reconcile gross findings reported in the NDA with those of raw data and histological findings. The seven mentioned exceptions examined grossly but omitted from histology also ignore a histological verification of the ante-mortem observations (when available) of the animal caretakers.

J) Histopathology - Examinations are claimed for 71/160 rats with satisfactory data. 75 animals had slides prepared by IBT which are now in the hands of Syntex (see slide inventory, supplement III). There are 68 TBA/TDA (or NTT) rats where Syntex refused to consider any histological data. With 8 rats excluded (see section B) about 9 rats are still unaccounted for.

Syntex has the original 75 slides and we understand also the blocks from which they were made. Instead of having their pathologist reexamine this material reliance is placed on the original data sheets of Richter and Gordon. If we had any assurance that Richter examined all the tissues on each slide and commented only on the adverse ones, would have indicated in the recording form any missing tissues, had the gross pathology accompanying each case available (including any indication of the autolytic state if any), had been given access to all tissues from all animals (rather than just 64/160) we could have some faith in the data. The reading of some tissues by Gordon of some tissues and special GI examinations only complicates the situation as Gordon's slides are not available to Syntex, there may be variances in pathological judgement between the two pathologists and in part these were done after the report was submitted to IBT (and so not included in the FDA submission). Distribution of the Richter material for histopathological examination was from 18 controls, 20 T-1 19 T-2 and 7 T-3. Gordon's specimen came from 4 control no T-1, 4 T-2, and no T-3 rats. The distribution of examinations among the treatment groups can hardly be considered as representative.

K. Histopathology Exception Report - It is claimed that except for the lipoma in #100 all the findings discussed are in the IBT report. This section tries to note the observations in one part of the IBT report but not in another and those found in the IBT report and not in the summary (or vice versa). It was in part these inconsistencies that led to the FDA inspection and secured the raw data at IBT. No explanations are offered. These must come from IBT and not Syntex, if any exist.

L) Pathology Findings in 8 Rats with Irreconciable Discrepancies - #4, 53, 55, 76, 87, 102, 119 and 131 are noted as having no atypical findings. (8/8 have gross lung pathology; stomach hemorrhage and dark foci are noted in two of T-2 group). Important histopathological findings relate to the adrenal congestion and telangiectasis (1/3), liver changes (2/3) pituitary hyperplasia (1/3) stomach necrosis and hemorrhage in the T-2 group in our evaluation of this group.

M) Tumors - To test for tumogenicity FDA now suggests studies over 24 months in rats at elevated dosage. Syntex makes a claim that 107 rats completed 16 months or more and 87 18 months or more.

Using their reconstructed tables B17-24 we note the following survival rates which do not agree with the above statement (see table below). At 18 months only about 50% of all rats are still alive. If the controls are discounted there are 69 rats on drug at 16 months 58 at 18 months and 28 at 22 months. (None at 24 months of course). We consider these numbers to be inadequate to measure the carcinogenic potential of the drug.

Group Identification	16 Months	18 Months	22 Months	24 Months
Control M	12	12	6	0
Control F	13	11	10	0
T-1 (2 mg/kg) M	13	11	4	0
T-1 (2 mg/kg) F	18	16	13	0
T-2 (10 mg/kg) M	13	10	3	0
T-2 (10 mg/kg) F	16	15	7	0
T-3 (30 mg/kg) M	4	3	0	0
T-3 (30 mg/kg) F	5	3	1	0
	94	81	44	0

It is clear from this and other data that the male rats are more susceptible to an early demise.

Syntex comments that in-life observations can detect only superficial tumors and fails to distinguish them from hematomas and abcesses. Their usefulness is in direct relation to the quality work performed by the technician in examining the animal and recording accurately the findings. Only poor observations and only over a limited time are available in the ante-mortem observation records. These are completely discounted by Syntex in that they require gross and histological examination for verification and tumors are always seen on gross necropsy anyway. With the true number of accurate necropsies in question these observations are not confirmable. Table M1 attempts to reconcile in its comments those which are at variance in the IBT report. Rat #59 was detected on necropsy as having

a growth but that was not histologically verified and dropped from IBT tumor table. #100 had actually two tumors according to Syntex a keratoaxanthoma and a lipoma that was missed in IBT tumor summary. M2 lists further tissue hyperplasias which are not counted as tumors. This list includes the pituitary 'adenomas' which tended to be more frequent in the control group.

In view of the "alert" given to us by the Ciba-Geigy Corporation on July 21, 1976 (see memo of M. Hein of July 30, 1976), a determination of tumorgenicity potential/carcinogenicity from naproxen is now even more vital. The data in M1 is inadequate to arrive at a conclusion as to this potential for naproxen. The tumors reported were of various types and included 2 in the control, 7 in the T1, 6 in the T2 and 3 in the T3 groups and raises the question as to how well they were looked for. These could only come from the 92 rats at best as 68 were listed as TBA/TDA (or TBA/NTT).

N) Urinalysis Evaluation - The data is limited to raw data from 3, 6, 9, 12, and 15 months. It lacks a pretest control and any data for 18 and 21 months. At these later times increased renal toxicity may well be expected. Data is presented for 4 parameters: Vol., Specific Gravity, albumin and glucose only. No microscopic, pH, ketones, etc., were looked for.

The data lacks specific identification of specific rats and are indicated only by sex and treatment group. Thus no correlation with pathology is possible. Also Syntex in their data analysis carefully avoids identification of the "n" involved. (10 were done when available, while protocol asked for five). Urine volume seems to be elevated at 6-12 months at the high dose level of drug. IBT in their report also included 22 month values which are not presently available as raw data and are said to have been typed into report directly from odd notes. (?)

The differences in calculations of mean from Syntex and IBT are minor for Spec. Grav. and Volume. Syntex listed the glucose and albumin in full form as the averages quoted by IBT are misleading.

O) Hematology and Blood Chemistry - Syntex admits to no raw data being available now and suggests that the data was entered into the report directly (??). The data in the IBT report is thus all that is available at this time.

P) Opthalmology - Syntex states that no slit lamp or opthalmology exams were done in-vivo and none are reported by IBT. Protocol had called for repeated examinations. The individual who normally performed such tests for IBT was given to us at time of inspection. At that time we were led to believe that such records for this study had existed at one time, but could now not be found by the IBT people.

Q) Summary - This is a listing of the data used in the 'reconstruction'. It is suggested by Syntex that reworking of the data uncovered no material differences from IBT report and both are said to "demonstrate meaningful long term experience with naproxen administration in the rat".

There are a series of supplement sections which have been considered already.

I. Body Weights (Syntex data analysis)

II. Organ Weights (Syntex data analysis)

III. Inventory of the slides at Syntex on this study.

Volume II contains Appendices and Exhibits.

I. Drug Administration

Identification of the material sent for test to IBT*

Diet preparation (includes data for parallel 6 months rat study (15/sex/level)*

*Some of these records were not available at time of inspection.

Food left/and food offered - If we understand the methods there are many errors in arithmetic calculation on the raw data sheets starting March 17, 1971.

Food consumption records - Only a few can be identified due to lack of dating.

II. Body Weights (raw data)

III. Organ Weights - Original data and the set prepared for the IBT keypunch operator.

IV. Necropsy Log (Only one version)

V. Histopathological Records - Reports from Richter and Gordon (Gordon has two which we in part have not seen in the past).

VI. Urinalysis (raw data forms)

VII. IBT report to Syntex January 4, 1972. This includes the J. Plank summary and the supportive tables.

VIII. Curriculum Vitae

Listed are:

Name	Apparent Function in the Study
J. Calandra, M.D., Ph.D.	President and Director of IBT Med. Dir. of Nalco (parent company of IB

M. L. Keplinger Ph.D.	Asst. Lab. Director 1968-70; Manager of Toxicology since 1970
W. Richter, DVM	Assoc. Prof. of Comp. Pathology, University of Chicago
O. Fancher, Ph.D.	V. Pres. and Director up to 1970; Scientific Director 1970/1, Consultant to IBT since 1971
Lester Happ	Group Leader of Necropsy Unit and Histology Dept., Tissue processing, organ weighing
James B. Plank	Group Leader Rat Toxicology Dept. - one of report writers also.
Philip S. Smith	Asst. Toxicologist and Coordinator of Toxicol. Studies 1/71 - 8/71 only.
Paul L. Wright, Ph.D. (Biochem)	Section Head Toxicology, Rat and Dog Dept. only after 3/71
Alexander Sutherland	Chief Histology Technician 2/71 - 4/72 only
Donald H. Jenkins, DVM	Manager of Wedge's Creek Research Farm Div. of IBT (is this breeding farm for toxicology study animals?)
Donald Greco	Group Leader, Clinical Chemistry
Donavan Gordon, DVM	Vet. Pathologist (Started with IBT September 1971)
Michael Black	Technician Rat Toxicology Dept. (necropsy, weighing of animals, caretaking, data assembly).
Other technicians	i.e., Marylou_____ are not identified.

Additional Comments and Evaluation:

1) Syntex has completely 'reworked' all available IBT raw data in an attempt to present as favorable a picture as possible of this study. In the process some data was reordered (i.e., weight data) or rejected (i.e., some histo data on autolysed animals).

2) In the "reconstitution" process using weight data some parts look reasonable, but without definitive proof. Other suggested reordering is implausable based on consideration of pre and post weight data.

3) As antemortem observations, i.e., "tumors" were not verified at autopsy or observed over much of the study, perhaps the identification process is only a help in fixing the most likely date of death to correlate with the other data (i.e., necropsy log, summary, survival rate data, etc.).

4) It is claimed that caging mixups were limited to adjacent cages. This did not always follow in the Syntex 'reconstitution'. Some are not explainable and may involve intergroup switches. Proof for later is only clear in #20-21 case where sexual identity was the clue.

5) Even after Syntex reordering there are many weight values at various dates in which prior and/or post weights for that rat are suggestive of improbability. We suspect here recording errors or further animal cage mixups. Some, but by no means all, have been identified by Syntex as 'nonconforming' values. They nevertheless were included in group mean calculations. (Means even after reordering do not carry a standard error).

6) Analysis of weights of specific animals suggests rapid weight loss when none may be expected (i.e., in controls). This may reflect poor husbandry practice, i.e., lack of food and/or water or disease. Some of these terminated before end of study (see for example #5 and #20) and were listed as TBD/TDA. Pathology listed in tables of Section G suggested respiratory death, a finding not possible in autolysed rats.

7) It is argued that if rats are identified with each treatment group correctly it matters little which is the true identity of each rat. The correlation of anti-mortem observations by caretakers with urinalysis data, possible rapid weight loss with histological, gross pathological and biochemical findings cannot be made.

8) Syntex seems to now admit that no opthalmology exams were made antemortem and no records to this exist. The post mortem eye exams are woefully inadequate to test opthalmological toxicity especially with the high autolysis incidence and absence of proof that eyes were looked at by pathologist in each instance.

Recommendation - The 'reworked' 22 month rat study remains unacceptable to demonstrate—

A lack of

1) toxicity to various tissues after administration of drug over a major portion of the animal's lifetime.

2) That naproxen had/or has not a carcinogenic potential which would require specialized trials for carcinogenicity in larger populations.

3) The identity of each animal with correct findings. Dates of death have not been satisfactorily demonstrated to this reviewer.

4) Certain provisions of protocol were not adhered to. Some are and some are not very important. We consider opthalmology exams with slit lamp exams in at least one species over an extended time as essential. Long term hematology in a drug affecting clotting is also vital.

5) Excessively high autolysis rates and weight variations within groups attest to low quality of animal husbandry without which no scientific merit can be ascribed to study.

In the absence of other animal studies extending over the major portion of an animal's lifetime and for a drug that may be used chronically for severaly years and in which a question of carcinogenicity has been directed to us, we have to recommend that Naproxen be removed from marketing immediately until such time as a 2 year toxicity study in rats is repeated, reviewed and found to clear any suspicions we now may have.

Manfred M. Hein

Manfred M. Hein

cc:
Orig IND
Orig NDA
HFD-150 IND
NDA
HFD-108
HFD-100
HFD-1
HFD-150/MMHein
Final typed by slt:8/31/76

NDA File - 150

Associate Director for New
Drug Evaluation, HFD-100

September 2, 1976

Deputy Associate Director for
New Drug Evaluation (Scientific)/HFD-101

Syntex Meeting - Naproxen

I decided that just for the record I would transcribe my notes on the nine reasons which the Syntex representatives presented for not taking naproxen off the market on the basis of the findings of the rat study at Industrial Biotest Labs. These were as follows:

1. The rat study was submitted in 1972. Some of the discrepancies found in that study were available to EDA in the NDA and were not found at that time.

2. There were no differences in expected human experience with the drug from the time it was approved until the present.

3. Syntex representatives feel that the studies in excess of 6 months duration are not required for approval of a drug of this nature (D'Aguanno disagreed vehemently).

4. The rat is not an acceptable model for man.

5. Additional clinical toxicity studies have been conducted in the rhesis monkey, the mini pig and the mouse. The 12 month study in the mini pig may be the closest model to man. There was no organ toxicity beyond expectation found in any of these studies.

6. Animal toxicity provides facilitating information for new drug approvals not, like human experience, paramount.

7. Syntex has perspective human trials ongoing which will continue for the next two to three years.

8. A restrictive action taken on the use of the drug by FDA will create anxiety in the population on whom the drug is being used and such anxiety may have a greater potential for adverse effect than the drug itself.

9. Syntex indicated that it would immediately begin a new 2 year rat carcinogenicity study in 800 animals in its own facilities. They further indicated that they will extend and closely monitor their ongoing human trials.

Dr. Finkel - 2

Art Levine asked that these statements be documented in the letter which Syntex is supposed to send to us, however, I think it is probably worthwhile having some record of our own impressions of these reasons.

Jerome A. Halperin

cc:
NDA File
Dr. D'Aguanno

JAHalperin/HFD-101 md 9/2/76

10/4/76.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. 76N-0411]

NAPROSYN TABLETS

NOTICE OF OPPORTUNITY FOR HEARING ON PROPOSAL TO WITHDRAW APPROVAL OF NEW DRUG APPLICATION

The Food and Drug Administration (FDA) proposes to withdraw approval of the new drug application (NDA 17-581) for Naprosyn (naproxen) Tablets held by Syntex Corporation, 3401 Hillview Ave., Palo Alto, CA 94304, on the ground that it contains untrue statements of material facts. Any request for a hearing or comments must be submitted on or before (insert date 30 days after date of publication in the FEDERAL REGISTER).

Naproxen is a nonsteroidal anti-inflammatory agent indicated for use in the management of rheumatoid arthritis and thus intended for long-term administration when appropriate. NDA 17-581 authorizing marketing of Naprosyn brand of naproxen tablets was approved on March 11, 1976. The application contained statements regarding studies of the long-term toxicity of Naprosyn which represented the drug to be safe for chronic human use.

The Director of the Bureau of Drugs now has reason to believe that certain material facts either were misstated in the application for Naprosyn or were omitted from the application. As a consequence, the agency's evaluation of the safety of Naprosyn was based on erroneous

data. Therefore, the Director is proposing to withdraw the approval of the application for Naprosyn.

BACKGROUND

The new drug regulations require that an NDA contain full reports of adequate preclinical tests by all methods reasonably applicable to show whether or not the drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling. The reports are to include all studies made on laboratory animals, the methods used, and the results obtained. 21 CFR 314.1(c). The NDA form itself states that the application may be refused unless it contains full reports of such preclinical tests and unless those tests adequately take into consideration such special factors as whether the drug is intended for long-term administration. 21 CFR 314.1(c), Form FD-356H, paragraph 10a, b.

This regulatory requirement supplements section 505(d)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)(1)), under which the Commissioner of Food and Drugs shall, after affording the applicant due notice and an opportunity for a hearing, refuse to approve an NDA that fails to contain evidence of adequate safety testing by all reasonably applicable methods. Protection of the public health, as well as the strictures of the act and regulations, requires that new drugs lacking evidence of adequate tests of safety not be permitted on the market.

The act also provides for the withdrawal of approval of an application that contains any untrue statement of a material fact. Section 505(e)(4) (21 U.S.C. 355(e)(4)). Among the grounds on which an application may be deemed to contain an untrue statement of a material fact is the omission from the application of any information obtained from investigations as to safety if such omission prevents a proper evaluation of the safety of the drug. 21 CFR 314.12(b)(1). Likewise, the misstatement, whether inadvertent or not, of significant data from which conclusions as to safety are to be drawn must be deemed to constitute an untrue statement of material fact.

ANIMAL STUDIES

Because Naprosyn is intended for long-term administration to humans, one test essential to a determination of its safety is a long-term animal toxicity study designed to measure the effects of chronic exposure to the drug over a substantial portion, or all, of the life span of the animal. It has long been the policy of FDA that an NDA for a drug intended for chronic administration, i.e., more than 6 months, is not approvable unless the preclinical tests include a long-term rodent toxicity study. This policy is widely recognized among drug manufacturers and has been enunciated publicly in speeches made between 1968 and 1972 by Dr. William D'Aguanno, Chief Pharmacologist of the FDA Bureau of Drugs, and in publications. ("Drug Toxicity Evaluation--Pre-Clinical Aspects," FDA Introduction to Total Drug Quality, U.S. Government Printing

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Office No. 1712-00220, Nov. 1973, pp. 35-40; and "Drug Safety Evaluation--Pre-Clinical Considerations," Industrial Pharmacology, Vol. I, S. Fielding, ed., Futura Publishing Co., Mount Kisco, NY, 1974, pp. 317-332.)

To comply with this requirement for Naprosyn, Syntex submitted the results of one study, a 22-month chronic oral toxicity study in 160 albino rats carried out by Industrial Bio-Test Laboratories (IBT) of Northbrook, IL, under Syntex sponsorship (the "IBT rat study"). That study was used for evaluating both the chronic toxic effect of the compound and the likelihood of its having carcinogenic potential. Two other long-term animal toxicity studies (a 12-month study in the mini-pig and 39-week study in the rhesus monkey) were not adequate to answer these questions because they were not carried out over the major portion of the life span of the animals, and they did not involve a sufficient number of animals to permit a meaningful assessment of carcinogenic potential. The clinical trials and usage to date are also not sufficient to assure long-term safety or lack of oncogenic potential; only a relatively small number of patients have received the drug for as long as 3 years, while the latent period for chemical carcinogenesis in humans may be 10 years or more. Furthermore, clinical experience is an insensitive indicator of carcinogenic potential of drugs.

The agency's assessment of long-term safety underlying the approval of NDA 17-581 was based, therefore, exclusively on the

IBT rat study. The materiality of this study and the data reported to FDA is evident from the fact that without the study, Syntex's application would not have been approved, for it would have failed to meet the agency's requirement of adequate long-term animal toxicity data to show whether Naprosyn is safe for chronic use.

UNTRUE MATERIAL STATEMENTS

FDA scientific and regulatory personnel have recently conducted an investigation of the circumstances of performance and the laboratory records of the IBT rat study. On the basis of this investigation, the Director of the Bureau of Drugs has determined that the report of the study submitted to FDA contained serious discrepancies from the records of the study held by IBT, and that other significant information concerning the study was omitted from the reports in the NDA. The Director of the Bureau of Drugs therefore finds that the report of the study in the NDA contains untrue statements of material facts that render the report uninterpretable in documenting the lack of chronic toxic effects or carcinogenic potential of the drug and thereby vitiate the earlier conclusions reached by the agency regarding the long-term safety of Naprosyn. Specifically,

1. The original NDA submitted by Syntex represents that the IBT rat study contained a sufficient number of animals for which records pertaining to necropsy, urinalysis, hematology, histopathology, general animal condition, and feeding and weight data were

available to permit an adequate evaluation of the long-term toxic and carcinogenic potential of the drug.

Instead, the original laboratory records revealed that for no single animal among the 160 animals that began the study was a complete set of such records maintained as required by the study protocol agreed upon by Syntex and IBT and submitted to FDA in the application, and that the extent of missing records was substantial and serious. For example, the protocol required daily examinations of all animals, with special attention to be given to the presence of externally visible tissue masses likely to be tumors; however, no systematic records of such daily examinations were available during the FDA investigation. Further, while the results of hematology, clinical chemistry, and urinalysis determinations and gross (readily visible without a microscope) pathology observations were reported in the NDA, the agency's investigation revealed no records at all to support the hematology and clinical chemistry determinations and only partial records on urinalysis determinations, body-weight values, and gross observations, ante and post mortem.

2. Syntex's submissions regarding the IBT rat study represented that a specified set of tissues had been examined histopathologically (with a microscope). In fact, laboratory records show that only some of these tissue samples were collected or prepared for examination. In addition, FDA inspection of the raw data in IBT's files disclosed

that, in certain cases, actual tumors were found in animals but were not mentioned in the submission, which is part of the NDA, and that the same was true with certain lesions other than tumors.

3. Withheld from the report submitted in the NDA was the fact that the majority of the animals observed post mortem had already entered a state of advanced autolysis or decomposition at the time of examination, rendering unreliable any gross observations made. Despite such unreliability, the NDA contains data on the results of gross observations of certain organs, and reports, for example, that the lung tissues of animals showed signs of congestion or, by a lack of attribution of findings, implies that the tissues examined were normal. The original laboratory records discovered at IBT indicate that the problem of autolysis was so extensive that, had it been made known to FDA during the agency's review and evaluation of the IBT rat study, this discovery alone would have rendered the entire study unacceptable in documenting the safety of the drug. In addition, many of the 47 animals described in one log kept by IBT as being "too badly autolysed, technician destroyed animal" were found to have certain gross pathologic findings ascribed to them in another log and reported in the NDA. Whether, in fact, these pathology observations were not made because of immediate discarding of the animals or instead were made in animals too badly decomposed to permit a reliable evaluation is not known, but either conclusion renders unacceptable the findings reported in the NDA.

4. An inspection of the records at IBT disclosed numerous inconsistencies with the report, which is part of the NDA, indicating that experimental animals were either identified incorrectly or were misplaced within and among the various treatment groups. For example, many animal weights were recorded as having been collected while the animals were alive on dates subsequent to their dates of death; several animals were recorded as having died on more than one date, usually with different versions of gross post mortem findings; extreme variations in body weight were noted both during successive weighings of the same animals and within any group of animals weighed at the same time, even though all animals were reported to have received standard care and drug administration. Such confusion with respect to animal identity renders unreliable any estimate of the onset and persistence of certain important toxic manifestations of naproxen, such as gastrointestinal ulcerations.

The applicant, Syntex, was made aware of these findings by a letter dated August 5, 1976, from the Director of the Bureau of Drugs. The company was more fully advised of the findings in a meeting held between representatives of the Food and Drug Administration and Syntex on August 20, 1976, during which the Syntex representatives acknowledged and discussed many of the discrepancies and deficiencies found in the report of the IBT rat study. Copies

of the letter and minutes of the meeting have been placed on file at the office of the Hearing Clerk, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852.

LEGAL BASIS FOR WITHDRAWAL OF NDA

When an approved NDA is later found to have contained untrue statements of facts which were material at the time of approval and which remain material when the untruth is discovered, the law requires that the application be withdrawn, after appropriate notice of opportunity for a hearing and the holding of such hearing if justified. In certain circumstances, statements of fact that were material to approval of an NDA at the time the agency evaluated the application may have ceased to be material when they are discovered to be untrue. For example, evidence invalidating a study that was essential to the original evaluation of the safety of a drug may not be discovered until years after the drug is approved and marketed, and under some circumstances intervening wide clinical experience or additional studies with the drug may be sufficient to resolve the questions of safety originally addressed by the study in question. In another possible situation, the Bureau of Drugs might determine that the studies that were required at the time of the initial approval of an NDA are not, in light of more recent toxicological standards, in fact essential to such continuing approval. An untrue statement in such information would not be regarded as material for

purposes of withdrawing approval of the NDA, notwithstanding that initial approval would not have been granted had the untrue statements been known at the time. In such situations, the Director of the Bureau of Drugs may decline to initiate withdrawal of approval of the NDA.

No such circumstances exist in this case, however. Naprosyn is not a long-approved or an extensively used drug. Moreover, the agency regards a long-term toxicity study as having been essential to the approval of the NDA for Naprosyn and essential to a current assessment of its safety, and thus as material. The Director concludes, therefore, that the misstated facts, which were material to the original approval of the NDA for Naprosyn and continue to be material, justify its withdrawal at this time.

In a proceeding to determine whether to withdraw approval of the NDA for Naprosyn under section 505(e)(4) of the act, the only issues are whether the statements in the application (a) were actually made, (b) were untrue, and (c) were material, and continue to be material, to the approval of the application. To justify a hearing on the proposed withdrawal of approval, Syntex must be able to show that there is a genuine dispute with respect to one or more of these issues. No other issues are germane to a decision to withdraw approval of an NDA on this ground.

Evidence supporting a claim that statements in the report of the IBT rat study included in the NDA were not untrue must demonstrate that the report as submitted was complete and accurate in all respects. This evidence must consist of original records, such as laboratory records, log books, and pathology slides which prove that the report is supported by the actual raw data and is therefore true.

Evidence supporting a claim that the misstatements in and omissions from the report of the IBT rat study were not material must demonstrate either of the following two propositions:

(a) That valid scientific conclusions can be drawn from the actual raw data generated during the study and therefore that the misstatements and omissions are not material to an evaluation of the study as evidence of the safety of Naprosyn for long-term use. Evidence to support this proposition must consist of original records, such as laboratory records, log books, and pathology slides which demonstrate clearly and objectively that the study was performed with the requisite number of properly identified animals, that adequate contemporaneous records were maintained, and that unequivocal scientific conclusions regarding the safety of the drug for long-term use can be drawn from the data obtained from this study. Hypothetical reconstructions of portions of the IBT rat study, such as those offered by Syntex representatives in the August 20, 1976 meeting, and plausible, but conjectural, explanations cannot suffice to demonstrate that the errors in the report are not material.

(b) That the IBT rat study itself was not material to the approval of the application at the time it was approved or is not now material to an evaluation of the long-term safety of the drug. Evidence to support this proposition must demonstrate either (1) that the study was not essential to the original evaluation of the safety of the drug; or (2) that intervening events since the time of approval, e.g., new scientific information derived from human experience or animal investigations or changing scientific standards, have rendered the study scientifically obsolete and therefore not material to a current appraisal of safety.

In the absence of a showing that such proof is available to demonstrate that the statements are not untrue or are not material, the statute mandates that FDA withdraw the NDA.

If approval of the Naprosyn NDA is withdrawn, Syntex may resubmit the application and may include either new data providing evidence of long-term safety from a rodent study completed since March 1976 or a resubmission of the IBT rat study. If the application is resubmitted, the Bureau of Drugs will determine whether the application is approvable under the statutory criteria set forth in section 505(d). If the Bureau finds the application to be not approvable, it would follow the customary procedures for denying an NDA, including providing Syntex with an opportunity for a hearing on the proposed denial. That process provides the proper

forum for assessing whether Syntex's attempt to reconstruct the IBT rat study provides an acceptable basis for determining the safety of Naprosyn for long-term use.

Accordingly, notice is hereby given to the holder of the new drug application for Naprosyn, and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)(4)), withdrawing approval of the new drug application and all amendments and supplements thereto on the ground that the application contains untrue statements of material facts.

If any person subject to this notice elects to avail himself of the opportunity for a hearing, he shall file on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), a written notice of appearance and request for hearing, and the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of the applicant and any other person subject to the notice to file a timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such persons not to avail themselves of the opportunity for a hearing, and the approval will be summarily withdrawn.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. For the purposes of such a hearing, the sole issue in this case is whether the application as originally submitted and approved contained untrue statements of a fact material to such approval and to a current evaluation of safety. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person who requests the hearing, making findings and conclusions and denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate and directed to the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852. Such submissions, except for data and information

prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk during working hours, Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-1053, as amended (21 U.S.C. 355)), and under authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: October 4, 1976

J. Richard Crout, M.D.

PALO ALTO, Calif., Oct. 14 --- Syntex stated today that it does not intend to withdraw its anti-arthritis drug, Naprosyn, from the market. The action by the FDA today gives Syntex an opportunity to request a hearing on whether or not sales of Naprosyn should be halted. Syntex previously announced that it intends to demand a full hearing and it repeated that today.

Syntex made a public statement on October 7, 1976 announcing that the FDA intended to take exactly the action which was taken today.

The FDA has not yet made a decision on whether to grant a hearing. Syntex stated that it believes that it is entitled to a hearing because there are significant issues in dispute and said that it will appeal to the courts if the FDA does not grant a hearing.

Dr. Albert Bowers, President of Syntex Corporation, stated "Syntex believes that there are sufficient scientific grounds to justify the continued availability to patients of this important and useful drug."

Dr. Bowers emphasized that Syntex is fully confident that Naprosyn is safe and effective. Dr. Bowers pointed out that the FDA action is based on alleged deficiencies in a rat study on Naprosyn performed by Industrial Bio-Test Laboratories, Inc. for Syntex between 1969 and 1971. It is the FDA's position that because of these deficiencies Syntex has not complied

OVER

with all requirements for continued approval. However, the FDA has not indicated that this study presents any evidence that Naprosyn is unsafe.

"The accumulation of scientific information -- numerous animal studies and extensive human clinical experience -- is the basis for the complete confidence of Syntex scientists in the safety and efficacy of this important drug," Dr. Bowers said.

The particular rat study involved in the FDA action was not required by the regulatory agencies in 39 of the 40 other countries in which Naprosyn is currently marketed. In these countries, approval requirements were satisfied by numerous other animal toxicity studies and clinical data.

Naprosyn was discovered at the Syntex Research Center in Palo Alto, California. It was first administered clinically in 1969 and subsequently has been the subject of extensive clinical trials in 15 countries. Total experience with the drug now exceeds an estimated 120 million patient-days of use. There are over 100 publications on Naprosyn in the scientific literature.

SYNTEX LABORATORIES INC.
3401 HILLVIEW AVENUE
PALO ALTO, CALIF. 94304

SYNTEX

Dear Doctor:

We thought it would be helpful for you to have a copy of a news release issued by Syntex on October 14, 1976 that clarifies the status of Naprosyn. The company issued the release as a response to an FDA press release on the same day in which the future status of Naprosyn was questioned. Subsequent reports in the news media have resulted in some confusion in the minds of physicians and patients. The enclosed statement explains our position in this matter. We are also enclosing for your reference, our Naprosyn package insert.

The important thing to remember is that Naprosyn continues to be available for your patients.

Sincerely,

James Strand

James Strand, M.D.
Director, Medical Department

FEDERAL REGISTER, VOL. 41, NO. 210—FRIDAY, OCTOBER 29, 1976

[Docket No. 76N-0411]

NAPROSYN TABLETS

Extension of Time for Submission of Data

In a notice published in the FEDERAL REGISTER of October 15, 1976 (41 FR 45605), the Director of the Bureau of Drugs offered an opportunity for hearing on the proposed withdrawal of approval of the new drug application (NDA 17-581) for Naprosyn (naproxen) Tablets held by Snytex Corporation, 3401 Hillview Ave., Palo Alto, CA. 94304, on the ground that it contains untrue statements of material facts. The notice provided 30 days for any person subject to the notice to file a written notice of appearance and request for hearing and to submit the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200.

On October 18, 1976, Syntex Corporation filed a written request with the Director of the Bureau of Drugs for an extension of time of an additional 30 days for the submission of data, information, and analyses on which Syntex intends to rely to justify a hearing, thus granting Syntex and all other persons who wish to avail themselves of the opportunity for a hearing a period of 60 days, as permitted by 21 CFR 314.200(c)(1)(ii), for submission of these data.

The Director has reviewed the request by Syntex and has decided to and hereby does grant the extension of time, thereby extending the date by which such data may be submitted until December 14, 1976. The date by which any written notice of appearance and request for a hearing must be filed remains November 15, 1976.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052-1053, as amended (21 U.S.C. 355)), and under authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: October 22, 1976.

CARL M. LEVENTHAL,
Acting Director, Bureau of Drugs.

[FR Doc.76-31615 Filed 10-28-76;8:45 am]

MEMORANDUM

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

TO : Frances O. Kelsey, Ph.D., M.D.
Director, Scientific Investigations Staff

DATE: JAN 05 1977

FROM : M. Adrian Gross
Scientific Investigations Staff

SUBJECT: Industrial Bio-test and Virazole

This summary is a compressed version requested by you of the considerations set forth at greater length in an accompanying memorandum on the same subject dated today.

The background of the problems we had with IBT-generated studies is highlighted in some detail with reference to four long-term animal studies there - Naprosyn, Isoprinosine, TCC and Virazole. The differences and similarities of these four cases are outlined and the conclusion that emerges is twofold:- the work carried out by IBT can hardly be said to inspire much confidence in its reliability and elements of criminal action appear to me to be associated with it.

In the case of Virazole there are some crucial distinctions from the othe three cases:-

a) we have recently been asked to inspect these studies following a refusal by HFD-140 reviewers to rely solely on reports by IBT;

b) it turns out that virtually all preclinical studies associated with this product (and all those that are completed) have been carried out by IBT;

c) unlike the case with the other three products, Virazole is the only one for which we have not seen the internal IBT records associated with their study.

A critical new development of which we learned yesterday is that our intentions to have Virazole studies audited has been transmitted to the sponsor and, we presume, through the sponsor to IBT.

We seem to be confronted with two choices here - either we audit these studies ourselves or we ask that the sponsor initiate such an audit and validation of the data process. Because of the event described above, I believe immediate action on our part is indicated.

Some projected difficulties with sponsor-audited studies are discussed in the companion memorandum. The gist of these consideration is that based on our experience so far, these investigations are not likely to be totally unbiased. Still, because of the scarcity of resources I can see

some merit in them provided we secure a copy of the raw data of any study to be validated by sources outside of the FDA before the validation process starts. This caveat would be especially important in such cases as with IBT where the likelihood of tampering with records cannot be judged to be negligible.

I believe there is precedent for this kind of precautionary action in the Searle investigation where we went considerably further to secure the integrity of data - actually sealing such records in situ. Since we are not empowered to take such action, I would recommend what every investigator carrying credentials of inspection is clearly empowered to do - copy the records.

In the companion memorandum two objections of yours are further discussed:- the possibility of records having been tampered with already and the possible issue of harassment claims by IBT. I would judge the first to be beyond our powers of estimation and the second one to be unjustified (if raised) due to a number of considerations listed there. In summary, I do not find your objections as being sufficient to override my recommendation.

MEMORANDUM

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

TO : Dr. Frances O. Kelsey, Director,
Scientific Investigations Staff, HFD 108

DATE: January the 5th, 1977

FROM : M. Adrian Gross, HFD 108

SUBJECT: Industrial Biotest Laboratories (IBT) and Virazole.

The following represents an answer to your request for written notes on the the essence of our discussion yesterday on this topic.

Brief Background of the IBT problem

Since April 1976 we have been involved with four long-term animal studies carried out by IBT:-

A) Naprosyn - review of a study on which we made an inspection and thorough audit of the raw data has led us to the conclusion that the study was unacceptable and we issued an NOH to withdraw the NDA on this product. At an informal conference held here on November 12th, 1976, IBT gave us a written response to Dr. Leventhal's letter to them dated September 25th, 1976. My review of this response is well under way at this time; I can conclude, however, at this date that absolutely nothing IBT presents there ought to change our impression that this study is unacceptable. Furthermore, it is my personal conviction that in the reports submitted to the FDA on that particular study, IBT had both withheld material information and substituted false information either of which could have affected our review. In my own mind, the evidence we have for this is overwhelming. It may also be worth noting that IBT's client for that particular study, the Syntex Corporation, is cooperating with IBT in furthering the IBT position vis-a-vis the FDA.

B) Isoprinosine - is another instance of a drug tested by IBT where we made an inspection and thorough audit of an IBT long-term animal study. Our findings are, in general, similar to those with respect to Naprosyn:- not only does the study appear to be totally unacceptable but evidence of causing false information to be submitted to the government is, to my view, present. Unlike the case with Naprosyn, however, I have no knowledge that IBT's client for that study, Newport Pharmaceuticals, has been informed of our problems with IBT concerning that particular work. I cannot assess, therefore, the degree of cooperation, if any, between Newport Pharmaceuticals and IBT.

C) TCC - an audit of a long-term animal study has been considerably hampered by IBT's initial refusal to supply the raw data, then by prolonged delays in supplying it, and then by additional delays in answering our requests for clarification. On December 14, 1976 they presented us with a new written version of that study. This is currently under review in SIS by Mr. Britten and I would estimate completion of his review in approximately two-three weeks. Preliminary indications at this time are that IBT had made false statements in their original reports submitted to the FDA, and it also looks as if that particular rat study (a "pivotal" one, we are being told) will be declared unacceptable at the conclusion of such review. I would also estimate that the chances of our discovering criminal elements in connection with that particular report are at least "good." IBT's client for that study, Monsanto, has been kept informed on our problems with IBT related to that work and Monsanto has attended at least two meetings we have had recently with IBT in connection with these problems. Their cooperation with IBT is hard for me to characterize; however, it is my firm impression that Monsanto is certainly not presenting to us a thorough, searching and critical report of their own audit (if any) of of IBT's records.

D) Virazole - Last June we were requested to inspect and audit certain IBT studies in connection with this product. At that time we were told by HFD-140 that at most a short-term IBT animal study had been submitted to the IND file for review. Although our audit was a rather superficial one, we did discover a number of irregularities in the conduct of that study. A more searching audit was deemed by us non-profitable at that time for two main reasons: we were simultaneously involved with a long term IBT study (Naprosyn) on a marketed drug product with which we became immediately concerned to a serious degree and, the opportunities for "lousing up" a short-term study are very limited even to an outfit like IBT. Since that time HFD-140 has brought to our attention a recently submitted long-term IBT study on this product as well as the information that all completed pre-clinical studies on this agent (including all the "Pivotal" ones) were carried out by IBT. As part of the follow-up of the inspection. Mr. Britten has reviewed the IBT reports on that study. He has found a number of inconsistencies which are highly suspicious. His overall conclusion in a memorandum addressed to me where his findings are detailed is that the study is unreliable as it is presently represented and that a raw data audit is necessary. I endorse both Mr. Britten's findings and his conclusions.

Recent Events in Connection with Virazole

Last month we received a request for an in-depth inspection and audit of IBT studies in connection with this product. I have also learned that Dr. Browder, the HFD-140 reviewer of that particular product, is declining to review any IBT reports without the underlying raw data having first been validated. I can share her concern in this matter and I would support her position that any scientific review and evaluation of unauthenticated reports by IBT (particularly long-term studies) is likely to be largely a waste of time.

In the meantime HFD-140 has complied with your request to provide a complete list of all preclinical studies carried out in connection with this drug product as well as to make available for us copies of past reviews by pharmacologists of preclinical studies on Virazole.

I have learned yesterday of a critical new development. It turns out that last week Dr. Browder in a telephone conversation initiated by the sponsor of this product, ICN, has informed the firm that she would not review IBT reports of studies (and, I emphasize again, these constitute all completed preclinical studies on that drug) until such reports are validated. Although, as I mentioned above, I share Dr. Browder's sentiments here, I believe her disclosing this sort of thing to ICN at this particular time was it not an error of judgment, at least an unawareness on her part of the likely consequences of such action.

What are these consequences and why are they important?

It is more than probable that ICN has by now or will shortly contact IBT for "clarifications" in connection with these studies. Thus, our interest in long-term or other pivotal IBT studies on Virazole will have been signaled to IBT before long. Given IBT's track record of not being entirely candid with us as well as their current embarrassing situation both in the FDA and, in general, throughout the pharmaceutical industry, and given the potential for great economic loss to them if additional "bad news" will surface, I would judge it to be not inconceivable that IBT personnel might burn the midnight oil in destroying incriminating records or making up new (more favorable) ones, or in general "tampering" with such records. This would be a very serious situation since, in addition to the direct concerns of Dr. Browder and the rest of HFD-140 (the "safety" issue for the drug) we also have to address the problem of possible fraud in connection with IBT. I should think it is imperative that we move promptly to forestall or limit such likelihood, that a potential criminal investigation of IBT could be severely jeopardized by such possible action on IBT's part.

In connection with the general concept we have batted around for some time now, that a sponsor of an IND or an NDA who had some of its preclinical work carried out by an "outside" (contract) laboratory should be required to validate (authenticate) himself such work if we declare we have encountered problems with other studies carried out by that laboratory, I have a simple observation to make: judging by the sum total of our experience in this area - Syntex (Naprosyn), Monsanto (TCC), and Searle (Aldactone and Aspartame studied by Hazleton and Experimental Pathology, Inc.) I have yet to see an instance where the sponsor has conducted an exhaustive such audit of the work of its contractor and has reported to us information which is prejudicial to that laboratory. It is perhaps naive to expect that this will ever happen given the obvious situation that the disclosure of such information will simultaneously prejudice also the product that was tested with the associated potential economic loss to the sponsor. Still, I can appreciate that this may be a poor substitute to the FDA doing all of the investigations and auditing,

but a substitute nevertheless since we cannot expend all of our resources forever inspecting IBT or others like them. This concept of industry validation of contract laboratories may not be the optimal solution, but it is a solution that even though it is likely not to work, we shall be forced eventually to adopt for lack of other practical alternatives.

Our recent experience with Syntex in this respect has taught us a lesson which any reasonable person could have anticipated. The sponsor of the drug will fight like a cornered tiger to salvage the integrity of the study at issue. As mentioned before, realities of life are such that we cannot expect such a sponsor to be as unbiased or as skeptical or critical of the work, as disinterested as we might be if we were conducting such audit. But although the battle we have going with Syntex shapes up to be a tremendous one, at least we are spared one important difficulty in that case: what is contained in the internal IBT records cannot be an issue between us and Syntex since they know we have a copy of all such raw data.

This would not be the case if we allow ICN to "cooperate" with IBT in re-evaluating the Virazole work unless we have a copy of the raw (internal) IBT records as they are at this time in our possession.

Recommendations for Immediate Action

We have, as I see it, two alternatives here: Either: a) we embark immediately ourselves in a thorough audit of at least some of the pivotal IBT studies on Virazole, or b) we allow ICN to conduct such an audit and report to us their findings provided we immediately secure a copy of the internal IBT records of such studies.

Although alternative (a) is the optimal one, I would be willing to go along with alternative (b) since I am always ready to be pleasantly surprised: I would like to see the first instance where a sponsor will present to us a useful and reliable validation report.

Possible Objections to My Recommendations Made Above

I cannot think of any objections to the need for having these studies validated which would be equivalent to indications for such validation.

In our discussion yesterday on this topic, you mentioned two possible objections which someone might entertain here:

a) given that IBT has already been alerted by ICN of an impending validation process (whether by ICN or by us) they may have already tampered with the original data so that our securing a copy of such data at this time might be rendered ineffective for our purposes. This is a possibility; indeed they may have done this; on the other hand, they may not have done this yet; it is also possible that they may not ever do this sort of ting since they are basically an honest bunch of people. This is also a possibility. But if they have been indeed honest on this issue up to now, I can see no harm in helping them stay honest by our securing copies of their data at this time.

b) Our sending an inspector either to validate or merely to photocopy the records could be interpreted by them as "harassment". I [illegible] doubt such possibility, but I do not believe that we ought to be unduly concerned on how IBT views such action. My own thought here is that, given the total picture as described in the "Background" section here and the potential public health menace that IBT represents, this firm has been treated with undue deference by the government at least up to now. Items:

-last summer, you may recall, I objected to a very unusual "understanding" that took place between IBT and Chicago District regarding future inspections. You may also recall that both you and Dr. Finkel endorsed such objections. We are some six months past that time now and I am not aware of any resolution of that problem where it seemed to me IBT was getting a very questionable kid gloves kind of treatment.

-although on November 12, 1976 IBT was asked to submit to us a list of all drugs and other products under FDA jurisdiction, and they promised to do so, we are nearly two months past that date and we have yet to be apprised of the first such item of information. I do not know that we are exactly beating on their door on this issue.

-although we have not kept secret our problems with IBT, I am unaware that the Bureau of Foods (which reviews many IBT reports on food additives in addition to having outright contracts there) has been overly concerned with the reliability of IBT-generated data. There may be other Bureaus in the FDA in this category.

-I do not know that the EPA is swarming with inspectors on IBT premises to check the validity of all the pesticide registration work carried out there.

-much the same can be said of the Department of Defense which had numerous and extensive contracts at IBT on experimental animal work in connection with the safety of radiologic preservation of foods. Such reports are now being reviewed and evaluated by the Bureau of Foods.

In conclusion, I would judge that IBT is not really entitled to claim "harassment" by the government if an inspector were to show up to copy some raw data in their possession.

Precedent for this kind of action

I would call attention to a similar kind of action taken last year by the Searle Investigative Task Force in the case of Aspartame where there was an analogous situation of "delayed" validation for specific (previously designated) studies deemed to be pivotal. Concerns about maintaining the integrity of internal records similar to those mentioned here had led in that case to the unusual step of sealing of such records in situ both at Searle and at their contracting laboratory, Hazleton. Since, as far as I know, we are not empowered to take this kind of action in situations like this if the company objects, I would not recommend this extreme step. However, I believe mere photocopying of records is something clearly within an inspector's right.

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Other Actions Which May be Indicated from a Consideration of these Issues

In addition to the recommendations for immediate action made above, I should think the following are worth considering for implementation:

1. Until such time that the Bureau of Drugs is willing to declare IBT work as being either of an acceptable or an unacceptable quality as far as its reliability is concerned, I should think it would be wise if all review of unauthenticated IBT-generated reports stop at least in NDE, if not throughout the agency. For those studies that are pivotal in nature an authentication process be initiated in each case.

2. If such an authentication process is carried out by the sponsor of the work, means of securing the integrity of the original records along the lines suggested here should be found.

3. Since IBT appears dilatory in submitting a list of drug products (and possibly other products under FDA jurisdiction) on which it has worked, and since they may claim they are not compelled to do this under the law, perhaps a compulsory means can be found - warrant, court order, etc. to achieve our aims. In seeking such order we could argue that we seem to be incapable in searching our files for an exhaustive such list and without this we cannot proceed with our mission to protect the public health.

MEMORANDUM

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

TO : Marion J. Finkel, M.D.
Associate Director for New Drug Evaluation, HFD-100

DATE: JAN 14 1977

FROM : M. Adrian Gross
Scientific Investigations Staff, HFD-108

SUBJECT: Review and Evaluation of the Syntex Submission in Response to our Notice of Hearing (NOH) to Withdraw the NDA on Naprosyn

The following are my comments requested by you on part of this submission; the part that is addressed here concerns certain Syntex statements referrable to the IBT study which was the subject of our June 1976 inspection. Most of these are limited to Section III starting on page 40 in the first volume of the Syntex response.

I shall skip over lightly the first 5 pages of this section which are merely introductory in nature and, to a large extent, of only peripheral interest: the qualifications of Syntex-hired experts who reviewed the "data", the problems experienced by Syntex' counsel, various Syntex opinions such that the "IBT study is adequate to fulfill the purposes and support the conclusions of that study." In this connection, I may pass on the following interesting item of information which may have been overlooked in previous discussions:

At the time of our inspection of Syntex last July in connection with this study we asked Dr. Hill, the principal toxicologist at Syntex and the man responsible for letting the IBT contract as well as evaluating its quality, whether he was satisfied with the work carried out by IBT. He replied that he was not, even though he thought the study was valid. He also stated in reply to other questions from us that he would not let another contract to IBT based on his experience with that particular study and that in fact he has not let another such contract since that time.

I shall not comment on other opinions expressed by Syntex such as whether the Agency has or has not made a prima facie showing of any untrue material statements, whether the Notice is or is not ambiguous or other such "legal" positions assumed by Syntex. Subsection A starting on page 44 begins with copying the first FDA allegation. Page 45 in its first paragraph is additional "legal" type of material.

Paragraph 2 on page 45 refers to the protocol for the study clearly not requiring record retention. Whether such protocol (a document of understanding or contract, drawn up between Syntex and IBT) did or did not specify retention of records is irrelevant in my view since the FDA does not ordinarily "preclear" protocols for preclinical studies, and, as far as I know, no such "preclearance" was sought by Syntex or IBT in this case. The protocol for this study was submitted by Syntex to both its IND and NDA for Naprosyn. Regardless of what any such protocol does or does not specify, the FDA expects records of studies to be maintained for inspection; at least this is our basic assumption in any inspection where the review of such records is the primary (often the only) means we have to validate or assure the reliability of what is being reported to the FDA. We have taken the position as far back as I can remember that, without such original records of observations, we have no basis of confidence in the reliability of the data reported to us.

What such records indicate to us is whether any such observations as were reported to us were in fact made, if made, whether they were made at the time they are alleged to have been made, whether the observations reported to us are consistent with the actual observations made, who made the observations, who made corrections in these observations, what is the nature and reason for such corrections, etc.

What is stated in the last paragraph of page 45 ("neither Syntex nor IBT have ever been asked, prior to 1976, to retrieve supporting raw data and records for such a study") appears to me to be irrelevant particularly in view of the fact that neither of these firms were inspected in the past "for cause" within the context of a preclinical study in need of a detailed audit.

Page 46, paragraph 1: I cannot comment on what IBT is said to have assured Syntex and I fail to see the relevance of this point. But one may ask a pertinent question here: If indeed it is true, as Syntex alleges here, that the records were available at the time this report was drafted, why did not Syntex make any attempts to examine such records to assure themselves that the data reported by IBT were indeed reliable and truthful? We have been told by Dr. Hill of Syntex (the man in charge of this study) during an inspection last July that no such attempt was made by anyone at Syntex during the period between the initial IBT report having been received by Syntex and the acceptance of the final version after corrections to be made by IBT were suggested by Dr. Hill. Dr. Hill also complained to IBT that the initial report was, in his view, unacceptable in that it did not present a sufficient amount of the underlying data. It was only after Syntex insisted on such specific data that Appendix II as well as other information was incorporated by IBT in their final version of this study, the one submitted by Syntex to the FDA.

The large paragraph on page 46 deserves some comment: given what the protocol required in connection with ante-mortem observations ("general condition and behavior-daily"), given that this protocol had been submitted by Syntex to their IND and NDA on Naprosyn, and given that the condition of the animals and their behavior cannot be ascertained without their examination, I do not see that the Notice (in its reference to daily examination) is inappropriate. We have indications that externally visible tissue masses likely to be tumors were present in this study, and this cannot be thought of as something unrelated to the condition of the animals; yet it is a fact that there are no systematic original records of such examinations and findings. What we mean by "systematic" here is an entry each day that the tissue mass was present, and, if present, what was its anatomic location, size, color, shape, consistency, etc. and other information relating to its rate of growth or observations indicative of its likely malignancy status. We have seen what I would term "sporadic" entries of "T" (which we were told at IBT stand for "tumor") but as explained on page 4 of the Hein-Gross memorandum of 8/10/76, these notes were unsatisfactory and incomplete.

Furthermore, such entries in a record intended primarily for body weights can by no stretch of the imagination be considered as being systematic or useful. I hope Syntex will not dispute that there is not a single instance that we know of any examination of the animals (daily, weekly, monthly, yearly, etc.) where there were no changes found in the normal condition and behavior of the animals and yet a record of such an examination can be shown to have been made. There is, therefore, vast room to doubt that the bulk of such examinations (implied by the protocol submitted to the FDA) were in fact made at all. It is not unreasonable to assume this if we think of yet another interesting feature: those animals for which the presence of an externally visible tissue mass is signalled in the IBT weight records by the appropriate symbol (T) at a certain date, but no such symbols are present at subsequent weighings (indicating that the tissue mass had regressed or totally disappeared) and yet pathologic examination reveals such mass to be present at the time of death of these animals; what are we to conclude on the fact that such observations were made at all, or, if made, on their regularity and reliability?

Page 46 concludes with a statement that certain observations were "in fact" made (note the caveat "except weekends" not present in the protocol submitted to the FDA) and I would ask here how does Syntex know such observations were "in fact" made daily? As far as inner ear infection (mentioned by Syntex) is concerned, this condition cannot be said to be absent without an individual examination of each animal. An animal with an inner ear infection detectable by individual examination for head tilting when the animal is standing, or by the animal's circling when suspended by its own tail may show no abnormal behavior whatsoever if merely looked at (as distinct from being examined) as it lies in some corner of a cage. At the top of page 47 we read of notations that were made on cage cards. Again, I wonder how can Syntex have first-hand knowledge of this? IBT had represented to us that the cage cards were lost.

Have they surfaced in the meantime? If so, where are they, who has them now and who else has seen them?

The last sentence in the first paragraph of page 47 can be dismissed, as I mentioned earlier, on the grounds that the presence of tumor is an integral part of the condition of the animal on test; the protocol submitted to the FDA requires that daily attention be given to the condition of the animals (at least this is the clear implication to me). If in fact this was not done, the FDA has been at least misled on this score. As mentioned earlier here, I would doubt not merely that "daily" examinations for tumors were made , but that examinations at any regular intervals for tumors were made in this study. It is a fact that there are no records of any such regular (systematic) examinations, and this is essentially what the Notice alleges.

A final comment with reference to the ante-mortem observations having been kept on the "cage-cards" now, unfortunately, no longer available:

Suppose we are willing to believe this assertion; how would it be possible to keep on such a card of at most a few square inches in area (a large part of which is occupied by the identifying number of the cage) records of daily examination that have to include at least many hundreds of dates (22 months study) to say nothing of any details of the findings? And if it is not, would Syntex still claim that such ante-mortem records of examination and observations were as useful as they themselves require in the conduct of their own animal experimentation?

Paragraph 3 on page 47 concedes the statement in the Notice regarding hematologic, clinical chemistry and urinalysis determinations. I am grateful for this. The fact that "individual values...are reported in the text of the IBT report" is in no way responsive to our concern. It is precisely these reported values that are in need of authentication by comparison with original records. As to the last "crucial point" in this paragraph, I shall leave it to our General Counsel to determine whether the retention of records issue does or does not represent an untrue material statement when viewed against the official form of the IND or NDA or both.

I find it unprofitable to comment again in detail on Syntex' "reconstruction" (bottom of page 47) of the body weight data beyond observing the obvious: Syntex cannot, anymore than we can, vouch for the reliability of all body weight means in the report submitted to the FDA - those for week 0 of the study, for each week from the first to the thirteenth and for each subsequent month. Without individual animal weight records (conceded to be absent) even IBT (the only organization directly involved in generating these data) cannot assure anyone, including themselves, on the reliability of the means reported by them. And without such original records, Syntex' involved "reconstruction" is no more than a tangled web of conjecture and speculation.

At best they can merely present a "plausible" version of what may have happened; as for myself, I happen not to be impressed with the likelihood of this scenario of Syntex representing the actual events that took place at IBT (see my memo to Dr. Kelsey of 8/30/76).

The fact that "the average weights from the periods for which original records are missing are consistent with the average calculated and verifiable for other portions of the study," (paragraph 1, page 48), does not provide much assurance of anything. If I were in a situation where I collected only part of the observations I was supposed to provide and if I felt impelled (or compelled) to "fabricate" the missing values, I can guarantee that these would not be "inconsistent" with neighboring values; if they were so, they would only be bound to attract additional curiosity, questioning and investigation.

Syntex' "determination"(?) that the values for the 8th and 9th week were recorded for weeks 10 and 11 (paragraph 1, page 48) respectively, speaks eloquently to me on the thoroughness of the research conducted at IBT at least at that time. I would not pretend that errors cannot occur in any situation, but it is just common sense that under any system with even minimum concern over the reliability of the data gathered, the most rudimentary process of supervision or "quality control" would have detected this sort of thing prior to its coming to the attention of the government. To give my personal assessment here, one may argue that it is perhaps not important or "material" from a scientific sense whether some weighing dates were transposed. What is important, however, is what this sort of thing indicates on the care exercised by IBT in any other weighing. Did anyone supervise the work of these technicians and check their findings? Can Syntex assure us in any tangible way other than by verbal statements from IBT that these technicians actually weighed these animals at any time for which there are no records, but where values are nevertheless reported by IBT?

In paragraph 2 on page 48 Syntex refers with certainty to an unverifiable situation: what was recorded on cage cards (all of which are said to be "unavailable" now) or on pathological observation sheets (of which only some 19% are available now). The logic near the end of this paragraph (the "same person transcribed..." theory) escapes me. We have been told that the "same person" (Mr. Plank) transcribed the information to Appendix II of the IBT report submitted to the FDA. In this transcription process we have signalled (Hein-Gross memorandum of 8/10/76, pp. 15, 16, 17, 20, 21, 22, 23, 24, 25, 26, and 27) a multitude of discrepancies between whatever is present in internal IBT records and what is in Appendix II. What we are saying here can be summarized as follows:

1) the fact that "the same" (meaning "only one") person was engaged in transcribing certain information cannot guarantee that such transcription is reliable.

2) even if we are to accept IBT's conclusion (the "same person" theory), of what relative merit is this situation where an internal record (not submitted to the FDA) was transcribed onto another internal record (also not submitted to the FDA) as against the very many discrepancies between what was submitted to the FDA (Appendix II of the IBT report) and the totality of IBT internal records?

The last paragraph on page 48 is characterized by Syntex to be a "legal point of view." What I read in it offends my common sense and I would ask a question here: If what is meant in the internal IBT records is at variance with what IBT reports, is not the reported information by definition untrue or false? Of course such inconsistencies are "correctable," but such correction process was not initiated by IBT before submission of the final version of its report or by Syntex before this report was submitted to the FDA. I am not prepared, however, to classify all such inconsistencies as "minor" nor am I willing to accept that all such discrepancies have been explained satisfactorily. What is "clear" about the "validity of the (IBT) report" in Syntex' view may be entirely different from what is "clear" in my own mind about this issue.

I am willing to accept Syntex' statement at the top of page 49 "that laboratory personnel as a general rule did that which was reported" in the sense that I believe the laboratory personnel at IBT were somehow involved with the animals said to have been on this test. It is the caveat "as a general rule" which concerns me: how well they performed their tasks no one at Syntex or at the FDA knows with any certainty. What we can glean about the character of such performance from the few records that are available is far from reassuring, at least to me.

At the bottom of page 49 we are being treated to another semantic pyrotechnical display which culminates with another "legal" statement: "there was, therefore, no 'untrue statement'..." in reference to the microscopic examination of tissues. I would disagree with this position of Syntex'. What are the facts here?

In both Appendix II (attached to the IBT report submitted to the FDA) as well as in the records where Dr. Richter or Dr. Gordon (the two pathologists involved in this study) entered their findings, there is a long list of organs and tissues for each animal. By not indicating those sections which were not examined, both Dr. Richter's and IBT's reports (they are not one and the same) improperly imply that such sections were examined, and were found to be free of any abnormalities. How do we know what sections could not possibly have been examined? By reference to the list of slides prepared by Syntex themselves. This entire issue is discussed in detail on pp. 29-31 of the Hein-Gross memorandum of 8/10/76, which Syntex acknowledges having received. By not challenging our statements, I take it that Syntex cannot dispute this part of the Notice. The specific instances Mr. Hein and I list here are, as explained in our memorandum, only a limited set of examples sufficient in our view to illustrate our point.

The first paragraph of page 50 refers to microscopic examinations in October 1976 and to the opinions of Syntex-hired experts. I have no concern with these. The issue of "materiality" of this entire aspect (mentioned at the end of this paragraph) is one that can be better addressed to those who have determined that the study under reference is unacceptable.

The second paragraph on page 50 deals with the tumors found in this study but which were not reported to the FDA. Syntex concedes here that there were such tumors. They again raise the issue of materiality for the umpteenth time and my answer has to be - of what value is a study where tumors found in the animals on test are not reported? Furthermore, are the four tumors referred to by Syntex the only ones which were not reported to the FDA? The Hein-Gross memorandum of 8/10/76, which Syntex was so insistent in having received, refers on its pages 19-23 to a much larger number of tumors or suspected tumors. I find no detailed discussion by Syntex of the problems signalled there. As mentioned above, the materiality of this issue is not for me to determine, but if anyone were to ask me, I would have to say this is material. Very material. Awfully material.

Page 51, first paragraph: more on Syntex' reconstruction and on the views of the "well-qualified experts" on which previous comments made here apply.

Page 51, third paragraph, contains an introductory sentence which does profound violence to my sensibilities as a pathologist: "The significance of gross findings depends on whether the gross observations were evaluated histopathologically, since gross pathological examinations are at best preliminary."

I would say that this kind of view strikes me as some form of perversity of widely accepted pathology practice: Gross observations are not merely "preliminary", they are the fundamental or basic ones for a variety of reasons obvious to any well-trained pathologist -

a) they are the only ones where the totality of the carcass of an animal and the totality of various organs and tissues can be observed; as opposed to this, histopathologic examination has as its object of reference only minuscule samples of tissue;

b) certain lesions such as abnormal discoloration of some tissues, certain ischemic processes, certain abnormal diffuse changes in size of some organ, abnormal relationships of some organ to other organs, certain pathologic states such as ascites, cachexia, dehydration, emaciation, certain forms of shock, congenital heart diseases and aberrations, etc. cannot be easily confirmed by histopathologic examination; some of these can never be so confirmed;

c) unless a thorough and searching gross examination has been made by a competent examiner who selects the samples of tissues for additional (confirmatory?) histopathologic study, the latter is of little if any value. If I were to choose between a situation where a pathologist has expended x units of effort (time) on gross examination only, and another one where the same pathologist had devoted 1,000 of the same units to histopathologic examination only, I would invariably choose the first alternative as the more useful or informative from a pathology point of view.

The second sentence in the third paragraph of page 51 reads: "In some instances where gross observations were made, no pathological changes were found when the organ was examined histologically, and therefore the gross observation was not material." This sentence, probably written by a lawyer (judging from its reference to materiality) betrays profound ignorance of realities in pathology. For certain gross observations of the kind that are signalled in the Hein-Gross memorandum of 8/10/76, such as pituitary adenomas the size of a large pea, large (externally visible) tissue masses, large tissue masses inside the body, grossly enlarged organs, etc. (pp. 19-27) failure to confirm such lesions histopathologically can be explained most likely on the basis of:

a) the person making the gross observation is either incompetent, or unreliable or poorly supervised or any combination of these; perhaps such person does not have a high regard for the truth;

b) no section from the appropriate organ was examined histopathologically;

c) a section from the appropriate organ was examined, but it was not representative of the affected part of the organ;

d) the section was collected but misidentified as belonging to some other animal;

I would say that any of these likely explanations for this situation would be disquieting, to say the least. To judge this sort of thing when it seems to be as extensively pervasive as we have seen in this study as being of no "material" importance in judging the quality of the performance here seems to be a bit much to me.

The introductory sentence of the last paragraph on page 51, I am sorry to say, is completely unintelligible to me. Of what relevance is this statement? What problem referred to in the Notice or elsewhere does it address? At any rate I would reject the last sentence in this paragraph continued on page 52:

"Since the conclusions from the study are based principally on the histopathological findings, these few incidences cannot be said to be of material importance." What about the FDA's "conclusions" and how does Syntex know on what these were "based principally"? The plain facts are that the FDA's original evaluation based on merely the IBT report (i.e. their version of the study findings) was such that this study was considered "acceptable." In such evaluation, I prefer to believe, all aspects of the study were considered. Now that we have additional information on this study gathered from records not originally submitted to the FDA, we have made a determination that this study is no longer "acceptable." This is due to a large number of reasons. Whatever "conclusions" IBT or Syntex or both drew from this body of data is of no more than ancillary interest to us.

The middle paragraph on page 52 is not responsive to what the Notice claims (referred to in the second paragraph of page 51): "the Notice further states that certain lesions other than tumors were not reported in Syntex' submissions.") Note carefully that "lesions" is not limited to merely "histopathologic findings" as in paragraph 2 on page 52. I can give several examples here from the Hein-Gross memorandum of 8/10/76:

Animals 59, 122, 118, 20, 86, 18, 143, 25, 113, etc. are all instances where lesions are described in internal IBT records to be present, yet no such lesions (or not all such lesions) are reported by IBT. This is by no means an exhaustive list of such cases.

The statement in the footnote on page 52 (referrable to paragraph 2) is misleading and it is sufficient for me to point out to a single such case:

Animal 86, is described by the pathologist to have had a histopathologically detected pyelonephritis yet this was not originally reported to the FDA (see Appendix II). Neither was it reported to the FDA that some 5 tissues from this animal were not examined histopathologically.

The fact that a reference to such a lesion may have been made in a summary (frequency distribution) of such lesions is not a justification for such omission for several reasons that will be discussed further down in this memorandum.

The paragraph at the bottom of page 52 refers to our statement, "not all microscopic findings of the examining pathologists were included in the IBT report." Syntex then proceeds to discuss just the two examples given by us - animals 55 and 111.

With reference to animal 55 they admit that the findings were not included on the pathology sheet in the NDA for that animal (Appendix II). They point out, however, that the findings were included in the summary tables of histopathologic changes. We are talking here about chronic nephritis in an animal that is said to have succumbed at 4 months. Note that the appropriate summary table of histopathologic changes in "post-mortem" T1 animals (page 53 of the IBT report) has no reference to which individual animals had what specific lesions; it is, rather, a "frequency distribution" type of table. Let us examine the nephritis problem here: the table on page 53 refers to 5 "post-mortem" males; from Dr. Richter's notes we can deduce that these are likely animals numbers 51, 53, 54, 55, and 59. The table on page 53 lists a total of three chronic nephritis cases (one of them focal). Dr. Richter's notes, however indicate for these five animals chronic nephritis for number 53 only and chronic focal nephritis for number 55 only, i.e. a total of only two cases. Thus, the summary table of histopathologic findings is not quite correct at least in this instance. Other instances:

a) For the control animals the summary table lists 4 "post-mortem" females and 10 "final sacrifice" females, a total of 14 animals. The pathologist's notes indicate a total of only 10 animals examined microscopically in this group (nos. 27, 28, 30, 32, 33, 34, 35, 36, 37, and 39) none of which are indicated to have died before the end of the observation period. Only one "post-mortem" control female is indicated to have been examined by him (animal No. 20) which is represented by the IBT report as being a male(!)

b) For the T1 females, the summary tables on pages 48 and 53 of the IBT report list 13 "final sacrifice" and 4 "post-mortem" animals in this group to have been examined microscopically. Dr. Richter, however, has reference to only 10 "final sacrifice" females (61, 62, 64, 67, 68, 69, 70, 74, 75, and 77) and only 2 "post-mortem" females in this group (66 and 71)

c) For the T2 males, the summary table on page 54 of the IBT report lists 7 such animals examined histopathologically; Dr. Richter, however, refers to only 5 animals in this group (nos. 81, 84, 86, 91, and 94).

d) For the T2 females the summary tables on pages 49 and 55 of the IBT report list respectively 7 "final sacrifice" and 6 "post-mortem" females examined microscopically. Dr. Richter, however, in his notes has reference to 8 terminal sacrifice females (104, 105, 106, 107, 112, 114, 115, and 119) and only 3 "post-mortem" females examined (one animal whose identifying number is illegible in his records, number 118 and number 102 the last of which he lists with the males in this exposure group). Note also here that the necropsy log does not refer to animal number 114 as being a "terminal sacrifice" animal; Number 110 is indicated in that log as being a "terminal sacrifice" animal, but this is not reported by Dr. Richter as having been examined.

As to the animal with the illegible number which I had assumed to be number 111 (see page 53) since it preceded number 112, I will concede that this may have been an unwarranted assumption on my part. On the other hand, Syntex' "conclusion" that this must be animal number 110, is bound to be wrong: a notation of "PM" is present for this animal in Dr. Richter's notes and animal number 110 (the necropsy log and Appendix II of the IBT report clearly tells us) was a terminal sacrifice animal.

I would summarize my comments on the last paragraph of page 52 (continued on page 53) with the following:

a) for animal 55, the FDA letter was correct - chronic nephritis (focal) was not reported where it should have been: on the reported list of lesions for that animal.

b) that this lesion may have been included in a frequency distribution (the summary table) is, to my view, not a valid excuse for such omission. The summary tables on histopathologic findings prepared by IBT and submitted to the NDA are markedly inconsistent with the actual data they represent and I would judge them to be at least unreliable if not downright false.

c) for animal number 111 I may have made an unwarranted assumption, but the "correction" of this number suggested by Syntex is bound to be in error. This issue cannot be satisfactorily resolved, in my view.

Finally, I am disappointed that Syntex does not choose to discuss here other similar instances, beyond the two examples given in our letter. There are many animals for which microscopic changes were noted by the pathologist (as seen in his records) but these were not reported on the list of lesions for each animal (Appendix II) or changes were reported but no such observations appear in the pathologist's records. A few additional examples of these kinds of problems: animals Nos. 9, 20, 22, 24, 25, 40, 48, 58, 74, 81, 83, 86, 94, 99, 100, 102, 109, 113, 118, 122, and 140.

In addition to this, the numerous instances of significant other notes made by the pathologist such as "no optic nerve" (examined) or "slide inadequate" (for examination) were not reported to the FDA in the list of the pathologist's findings. Also not reported to the FDA was even a single case of the numerous ones where the pathologists clearly indicated that he had not examined certain tissues. This particular situation can be illustrated by an extreme actual example: for animal number 74, 33 out of the list of 34 tissues (all except the bone marrow) were specifically indicated by the pathologist as not having been examined and the Syntex list of tissues indicates that slides of no tissues other than the bone marrow were in their possession. Yet this was not reported to the FDA in the original submission of the detailed findings for this animal (page 102 of the IBT report).

Pages 54 through 57 of the Syntex submission deal with the problem of autolysis. I would say that most of what I read here is non-responsive to our concern. The part of the Notice that addresses this issue is clear to me, yet Syntex appears (or pretends) not to understand what we are saying. Let us clarify this matter once and for all, particularly since this is one of the principal issues here:

Line 8 of paragraph 2 on page 55 and line 5 of paragraph 2 on page 292 (Syntex analysis of gross pathology) refer to the fact that the use of the acronym "TBD/TDA" was decided on by the "animal room technician" and this decision referred to this person "to necropsy the animal hemself." Am I correct in assuming that the "animal room technician" is a person other than the regular necropsy room technician? If so, is it further appropriate to assume that the main duties of such a technician is to see to it that the animals are fed and watered, that the cages are periodically cleaned, etc., in other words, that his "normal" duties are not primarily in the area of "necropsy"? Is it also correct to assume that animal room technicians do not come normally under the supervision of any pathologist even when they are engaged in pathology operations and that their training and experience in carrying out post-mortem examinations (necropsy) is somewhat short of extensive? If the answer to any of these questions is "yes", what are we to conclude about the reliability of pathology procedures in this study where we find this notation (TBD) for 55 of the 160 animals, i.e. slightly more than one-third of all animals and one-half of all dead animals?*

If, as I had previously assumed, TBD really means what we were told by IBT it means (too badly decomposed) and if this is completely equivalent to advanced post-mortem autolysis, I would repeat for emphasis here what I have said before about this study: if I were the FDA reviewer, and if this situation were known to me from reading the report on that study, this alone would have been sufficient for me to recommend against the acceptability of that study. This would be so even if we had no other doubts whatsoever on any other aspect of that study. A rate of 50% advanced autolysis in dead animals when this simultaneously represents more than one-third of all animals in a study is excessive in the extreme and it denotes nothing if not carelessness about observing the animals.

But now we find out things were much worse than we had reason to believe: we read further in paragraph 2 of page 293 of the Syntex "reconstruction" about the "factors" that went into the "animal room" technician's "decision to necropsy the animal himself": Quote: "Those factors include autolysis, time of day, day of week, technician's knowledge of the necropsy department's schedule (including workload), number of dead animals, etc. Autolysis, even though one factor, does not have to be in an advanced state to qualify an animal for designation TBD/TDA." End of quote.

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* According to IBT's report, (Tables XXIV to XXVII on pp. 47-51) there were 50 "final sacrifice" animals which leaves 160-50=110 animals having died during the study.

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What does this say? Starting with the "autolysis" factor, it says that autolysis need not be in an advanced state to have the animal examined in this cursory fashion. While advanced autolysis is an unavoidable, relatively rare event in a well-conducted study, it is at least a justifiable reason for a merely superficial examination. Autolysis that is only moderate in extent is less justifiable a reason for a superficial examination and one of only slight degree still less if at all so. So much for autolysis. What about the other "factors" mentioned by Syntex, such as time of day, day of week, workloads, etc.? I would submit that none of these in any imaginable way justifies a less than thorough examination by a competent observer.

The fact that these observers were likely less than well-trained and competent is not the only reason we have doubts on the thoroughness of their observations. Consider the following: paragraph 2 on page 48 of the first volume in this submission by Syntex attempts to persuade us that entries made on the necropsy log were made "without error." Yet for the 55 animals marked in this errorless necropsy log with the entry TBD - only one animal (i.e. less than 2%) had any kind of gross abnormality recorded. The exception was animal 146 for which a tumor was noted. Now I ask: what are the odds that a well-trained, competent and reliable observer doing a thorough examination of 55 animals dying with illness in a toxicity trial, would find any kind of grossly visible pathologic alteration in only one of these animals? My answer to this is that, in my experience, such odds are negligible.

If this is even approximately so, and if we keep in mind that the animals dying during a toxicity study are likely to include those most severely affected by the drug on test and/or those most susceptible to the drug's toxic effects, as well as what we said earlier here on the fundamental (crucial) value of the gross post-mortem examination, of what inherent informative value was this entire study? Again, my own answer to this question is that such value approximates the vanishing point.

Are these all the problems created by this particular aspect of the 55 TBD animals? Hardly.

I maintain that had IBT (and/or Syntex) even hinted in their submission at the existence of this excessibely large proportion of dead animals for which not a single gross observation was made other than a solitary tumor, we would have likely not accepted this study as a reliable one. I know that I certainly would not have. We are saying, therefore, without any equivocation whatsoever that in not disclosing this sort of thing, IBT and/or its client, Syntex, had withheld from us a highly material aspect of this work.

But, this is still not quite the worst aspect of this issue. It turns out that not only was highly material information shielded from our knowledge, actually downright false information of an enormous extent was substituted for it; this was done, in my view, to assure the deliberate deception process in which IBT and/or its agents engaged.

To better appreciate this, let us once more recall the key points of this particular problem:

The "necropsy log", it is alleged to us by Syntex and also by IBT in a separate communication, contained through an "errorless" transscription process all gross post-mortem observations observed in these animals, whether their source was "pathology observation sheets." cage-cards, "animal disposition forms," whatever. What this says is that there could be no information anywhere on gross pathology findings that was not present in the necropsy log.

Recall also that the original IBT report of this study as initially sent to IBT contained no detailed animal-by-animal list of gross observations. Syntex, however, (specifically Dr. Hill) returned this version of the study to IBT with the observation that this kind of report without details of the underlying data would not be acceptable to regulatory agencies in this country or elsewhere. He also had other suggestions for corrections.

After receiving Dr. Hill's communication, which amounted to a non-acceptability by him of the report as it was presented initially to Syntex, IBT made the corrections Dr. Hill suggested. I would add here, parenthetically, my view that I consider none of Dr. Hill's suggestions as being in any way inappropriate. Also in the second version of the final report by IBT there appeared what was not present in the first version of IBT's final report: Appendix II, a handwritten, detailed, animal-by-animal account of gross and histopathologic alterations said by IBT to have been noted in these animals. We were told during our inspection at IBT by Mr. Plank that the handwriting in Appendix II was his and that he himself compiled this detailed information.

Recall now what we have said earlier here - that in the necropsy log (supposed to contain the totality of the gross observations from any and all of the animals in this study) only one of the 55 TBD animals was signalled to have displayed any kind of grossly observed anatomic change at the post-mortem examination. In other words, for these 55 TBD animals (or perhaps only 54 since one of them was identified as animal number 360 when there were only 160 animals in the study) Appendix II ought to have contained no more than one animal with grossly visible lesions of any kind. The reason for this is that there could be no other source for such lesions that were not included (by transcription) into the necropsy log.

Furthermore, the evidence pointing to the apparently gigantic confusion on the identity of the animals on test does not rest solely on the "recording of body weights" (line 4 of the last paragraph of Syntex' page 58); the Hein-Gross memorandum of 8/10/76 (transmitted to Syntex) has numerous references to records of animals having died more than once. Unless Syntex is prepared to accept the notion that an animal can die repeatedly, the only other reasonable explanation would be that the records on this study were in a state of confusion (chaos?) or that the animals were misidentified. Either of these does not exactly heighten our confidence in the reliability of this work. Additional problems here are the numerous instances (and many examples are given in the Hein-Gross memorandum) of discrepancies as far as dates of death or experimental time elapsed until death is concerned between what appears in certain IBT records, what is relayed to the consulting pathologist, and what is reported by IBT, discrepancies in the set of lesions exhibited by individual animals, their state of autolysis, their sex, etc. etc. Syntex appears to be silent on the detailed problems discussed in that memorandum. I can also find no comments by Syntex on the related problem (also amply discussed in the Hein-Gross memorandum) of the discrepancies between one version of the necropsy log and another (mysteriously corrected) version of the same document. I would conclude this entire discussion with the thought that the few available records on this study do not convey to me a picture that this experiment was in anyone's control.

On page 59 there is a footnote; if the reference to the "IBT response" is the IBT document on this study dated 11/11/76 which we have seen, Syntex will probably not find our reaction to it very comforting to their point of view.

I shall skip over the initial part of the first paragraph on page 59 since it refers to certain assurances IBT has given Syntex and to "Syntex' independent evaluation" neither of which are any concern of mine. Out of mere curiosity I would ask what is meant by "independent" evaluation? Was Syntex not in communication or in a state of cooperation with IBT during this work?

A sentence in paragraph 1 on page 59 reads: "Drug effect in this study was seen and reported through comparisons between treatment and control groups taken as a whole, not between individual animals." I hope FDA reviewers will not incur the displeasure of Syntex if they are as bold as to attempt to form their own evaluation of the data reported in some study. I can conceive of a reviewer even going as far as to be skeptical of what a sponsor may or may not believe is a drug effect. In fact some reviewers have been known to read not only the sponsor's own evaluation, but they have dared to examine the individual animal data in order to assure themselves that the group averages have been properly computed. I would like to believe this kind of extreme behavior on their part does not upset Syntex who may be under the impression that someone has challenged their own conclusions.

We read further in the same paragraph: "The FDA should not now be allowed to complain that information pertaining to individual animals (as distinguished from groups of animals) which was not in the original report, is not presently available."

What is one of the principal problems with this work, as we have seen, is the information pertaining to individual animals (Appendix II of the IBT report) which was included in the original report by IBT only after insistence from Syntex (Dr. Hill's letter to which we made reference elsewhere here). The same is true with other information pertaining to individual animals which also was included in the IBT report, such as the tumor table on pp. 58-59.

In general, our conclusions on the quality of this study are based largely on the fact that these reported individual animal data as well as the reported group averages (computed from individual animal data and from nothing else) do not appear to be reliable when compared with the records that are available or their reliability cannot be assessed if the appropriate records are not currently available.

Paragraph 2 on page 59 contains yet other statements on which Syntex cannot have any direct knowledge; this is in reference to their "adjacent cage" hypothesis which Syntex was kind enough to unveil for us at the world premiere held here last summer.

The rest of page 59 deserves no comments since it is more on Syntex' "evaluations" and it is replete with generalities which say nothing, e.g. "many of the variations did not represent real weight differences," "frequently," "usually," "not unusual," etc.

Much the same goes for the middle two paragraphs on page 60: more speculations, what Syntex experts believe, etc.

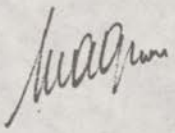
The final paragraph of Section A which starts at the bottom of page 60 is another non-sequitur; as far as I know we have never stated or implied that "gastrointestinal ulcerations could have been determined by the exact weight of an animal at a given time" or that "immediate sacrifice" or any other kind of "sacrifice" was in order in this study.

I regret that I cannot comment at greater length on Section B. The Syntex Reconstruction starting on page 61; large chunks of it are quite unintelligible to me. I also happen to believe it is a completely superfluous exercise since some of us are at least occasionally capable to analyze a set of data. What is our essential problem with the IBT study is not related to interpretation, analysis or evaluation of data but, rather, to put it quite bluntly, "what are the data." It is my position that Syntex cannot shed any useful light whatsoever on this central question which takes priority over all others concerning the data. We have transmitted our specific concerns over the data in this study to Syntex in the form of the NOH and, subsequently, in the form of much more specific discussions of the problems we perceive with the data in this study. I see nothing in the present submission by Syntex that in any way allays our concerns.

The only really new item of "data" here is the results of the additional histopathology study carried out, we are told, in October 1976. Unfortunately, I cannot comment in any meaningful way on this since I am not privy to the information on the "whys" and "hows" this particular set of tissues examined at that time was selected.

I have noted that during this October 1976 examination additional (previously unreported) tumors for the animals in this study were detected. This is the sort of thing that does not exactly surprise me, given what I am inclined to believe on the quality of pathology operations at IBT.

Finally, I must apologize for the quality of this review which may not be quite up to the standard that I aim at. One reason for this is that this work was assigned to me on 12/21/76 with a due date of 1/21/77 (30 calendar days). During the last three weeks of December I was absent due to illness; also earlier this week, after I had "budgeted" time for it, I was informed by you that the "due" date had been advanced to 1/14/77.



MEMORANDUM

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

TO : Associate Director for
New Drug Evaluation (HFD-100)

DATE: JAN 14 1977

FROM : Manfred M. Hein, Pharmacologist (HFD-150)

SUBJECT: Review of Data Submitted by Syntex in Relation to NOH for Naproxen
NDA 17-581

On December 15, 1976 I was given a set of 6 volumes submtted by Syntex in connection with their reply to the NOH on Naproxen, NDA 17-581. Since volumes 4 and 5 are primarily medical, review of volume 1, 2, 4 and 5 will also be independently done by Dr. A. Norris of HFD-150.

Enclosed please find my detailed analysis of volumes 1, 2, 3 and 6.

My overall impression is that the added material consisting of:

1. "reconstructed animal data"
2. Short term mutagenicity studies in unicellular systems in lieu of long term mammalian carcinogenicity studies
3. Supplementation of histology in 22 month toxicity study
4. A limited supplementation of previously established medical efficacy and safety
5. Testimonials by leaders in various aspects related to the subject
6. A study to try to validate histological examination in badly autolysed animals by IBT
7. Verbal arguments

does not change the recommendations made earlier; that until an adequate long term chronic toxicity (and carcinogenicity screening) study is completed, submitted and reviewed by FDA there exists inadequate preclinical safety information on which we would today approve a long term administration nonsteroidal anti-inflammatory drug for use in man.

Manfred M. Hein

Manfred M. Hein

NOTES ON MATERIALS SUBMITTED BY SYNTEX IN RELATION TO NOH DOCKET 76N0411 ON NAPROXEN (NDA 17-581) DATED 12/14/76

January 4, 1977

(NDA 17-581) dated 12/14/76

The material submitted consists of a reply to our notice of a hearing and an attempt to justify that there should be one. This is contained in Volume 1 of the submission and covers a total of 78 pages including the legal references and sign-offs. I received this and the other volumes below on December 21, 1976.

Volume 2 is a collection of expert opinions from:

J. Lederberg, Ph.D.
B. N. Ames, Ph.D.
S. Bloomfield, M.D.
H. Hodge, Ph.D.
L. Hollister, M.D.
J. T. Litchfield, Jr., M.D.
R. Richards, M.D.
F. Robinson, D.V.M., Ph.D.
D. Willigan, D.V.M., Ph.D.
G. Zbinden, M.D.

Syntex has supplied to each of the above at least part of the present submission and has asked them to comment on various aspects related to their expertise. Also appended to these testimonials are respective CVs, lists of publications and in some instances specific reprints.

Volume 3 is a reconstruction of the IBT 160 rat 22 months toxicity/carcinogenicity study. This study has been presented to us in 1971 as part of IND 5281;, in 1975 for the approval of the NDA 17-581; in recontructed form August 20, 1976 (with further amendments of August 31, 1976, September 3, 1976 and September 28, 1976). At this time there is still another reconstruction in that additional tissue sections have been imbedded from stored wet tissues and the slides subjected to examination by Dr. Richter, further data analysis has taken place and comments have been added by Syntex to the various sections of the original IBT report.

Volumes 4 and 5 related to medical studies, particularly those of longer duration and will be examined in this division by Dr. Norris.

Volume 6 is an analysis of potential carcinogenicity and a special IBT autolysis study designed to demonstrate that even though animals are autolysed there is still gross and histopathological information retrievable from such material. This was also shown to us by IBT at the time of their November 10, 1976 meeting with the Bureau.

A. General Comments:

1. The animal study data (as well as volumes 4, 5, and 6) are marked confidential and proprietary. It is our understanding that once an NDA is approved, as this was in March 1976, summaries of animal data are no longer treated as confidential. Also the distribution to various outsiders not connected with FDA or the Syntex company tends to raise the question as to whether data should be treated as confidential. Certainly this data is more complete than the reviews prepared by Gross and Hein which the Agency does not consider as original confidential trade secret data. (The subject of the legal action 76 2193 in U.S. District Court for District of Columbia.) A legal opinion as to what is confidential, the original IBT report, the comments and several reconstructions by Syntex, or both is in order. A report might be considered as a summary of raw data, as in the IBT case, if mean and not complete individual data is presented.

2. From the materials submitted it is suggested that the defense to be employed will include some of the following arguments:

   (a) Expert opinion of two or more experts in specific areas of expertise which may be asked to testify in response to each argumentative point which we foresee to be at least:

      (1) Maximal predictive information can be obtained from animal studies in any species by doing no more than 6 months of toxicity study.

      (2) General inability to predict from findings of animal studies to human trials.

      (3) A rat study lasting for 22 months and containing 160 rats cannot be considered as a carcinogenicity study or even a carcinogenicity screen.

      (4) As carcinogenic development involves mutation, tests for mutagenicity also test carcinogenic potential. Suitable mutagenicity tests thus are more suitable, because of numbers of observations involved, than in vivo animal studies that are carried out over the major portion of the "lifetime" of the animal.

(5) FDA has recently permitted other agents (including Motrin) to go on the market which involve long term administration with less than adequate (in number and/or duration) study in animal test systems if "Lifetime" and large numbers (i.e., 50 or more/test group) are considered.

(6) Tissue culture studies, "Ames Mutagenicity Tests", tests of yeast recombination, structural analysis of the basic chemical and its metabolites, dominant lethal tests and the testing of incidence of lymphoma in susceptible mouse strains are adequate and superior indicators of carcinogenicity.

(7) To do meaningful animal lifetime studies for the ability of carcinogenicity induction is going to require the use of several thousands of animals each most carefully studied which is an impossibility based on availability of facilities to do this with every agent, both those presently marketed and those that hope to be added to the FDA approved list.

(8) Recognized experts in the field have judged the IBT study as originally presented and certainly after the reconstruction as adequate to demonstrate long term toxicity.

(9) The present availability (in 1976-1977) of adequate well controlled long term clinical studies obviates the need for long term toxicity studies in animals.

(10) Even after there has been considerable autolysis it is still possible to perform a satisfactory histopathological evaluation of toxicity. This is to be demonstrated by using the IBT study on controlled autolysis.

(11) There being no formal guidelines ("cookbook") for the conduct of preclinical studies it has been possible for some of the drugs to go on the market with a lower volume of information on animal toxicity than other drugs (even if the indications are similar and use is for a similar duration of clinical use).

(12) Arguments to support the concept that a study can be reconstructed from the basic data making certain assumptions, suppositions and supplementing it with some new pathology data from stored tissues.

(3) It is obvious to this reviewer that such considerations are not limited to an examination of facts presented and "validating" the data and the statements made about them. Rather there are certain policy decisions involved which will have to be addressed by upper levels of management. It is in part this reviewer's aim to identify such issues and to alert FDA to the issues that are being raised. Also from personal knowledge obtained through the June 1976 inspection at IBT and the prior examinations of the reconstructed data (see reviews of August 10 and 30, 1976) it may be possible to offer some suggestions as to how to counter some of the arguments presented.

B. Analysis of Certain Statements Made in Volume 1 and Comments Regarding Them

Page 1

1. Paragraph 2. It is argued that the NOH contains no reference challenging that Naproxen is either ineffective or not safe. FDA maintains that the burden of proof for safety rests with the applicant in an NDA and it is their charge to convince us that it is safe. By disallowing the rat study in question FDA takes the viewpoint that safety over a long period of administration in man is no longer available and thus long term administration to man is no longer regarded as a safe procedure. It is a hazard to health.

2. Paragraph 3. It is suggested that the IBT study is immaterial based on new mutagenicity tests and clinical experience. If this were so, there would be no need for any long term toxicity studies in any animal species once clinical trial has been established in man, even if the information was generated in another country. (Note the bulk of the clinical data collected in support of this contention is from the UK). In regards to the mutagenicity tests, they have so far never been accepted as any substantiation that any agent is free from carcinogenicity. At best they serve as an index as to the priority for conducting carcinogenicity studies.

Page 2

3. Top paragraph. IBT in 1969 is promoted as a prestigious institution having done work for the FDA and other governmental agencies in the past and was in part selected on that basis. It may be advisable to check if IBT did indeed do work in the early 1960's for FDA. Dr. Hill has been heard to state after the study was completed that this was the only and certainly the last study that IBT would ever do for Syntex since he was not satisfied with the quality of the work.

4. Middle paragraph. The submission of the IBT report on March 22, 1972 is claimed to be a preclearance process for the NDA approval. This reviewer would suggest that it was rather in support of ongoing IND clinical trials in IND 5281. It is true that Syntex had several conferences and other contacts with FDA between 1972 and 1976. In view of Syntex's known misgivings about this study (Dr. Hill has claimed that he alerted FDA to his misgivings at the time the study was submitted), it is surprising that they never questioned FDA regarding the possible need for additional studies.

In the brochure prepared for the Arthritis Advisory Committee meeting by Syntex on February 27, 1976 regarding Naproxen the subject of preclinical safety is glossed over with the following statement:

"2.1.9 Summary of toxicology studies. Naproxen exhibits a low order of toxicity in single dose studies in animals. In acute and chronic studies in a variety of species the principal pathological effect is gastrointestinal irritation and ulceration. The lesions seen are predominantly in the small intestine and range from hyperemia to perforation and peritonitis." (Brochure was dated January 1975).

The committee, in making a pre-NDA review of the drug was apparently largely considering clinical matters and did not question the possible deficiencies in the toxicological profile as developed in animals. This is understandable as these committees are composed largely of clinicians which do not have adequate expertise to pass on other matters i.e., preclinical studies chemical controls, legal aspects etc.

In respect to the data alluded to on other animal species it is here pointed out that there also were:

(a) 12 months minipig study involving only 4/sex/level which was also performed by IBT about 1969. From this study Syntex should have been aware of the quality of IBT work and monitored the rat study better. It also refutes the claim that the rat study was the only contract given to IBT by Syntex.

(b) 9 month rhesus monkey study involving 4/sex/level which was done by Hazelton.

(c) 6 months study in mice involving only 5/sex/level performed by Syntex.

(d) It is notable that in this context there is no mention of the 6 months rat toxicity study also done by IBT concurrently with the study in question. This involved 15/sex/level. Whether certain information from this study was made part of the questioned longer rat study (i.e., body weights, food consumption data and possibly other parameters) is not established or proven as inapplicable.

5. Last paragraph. On June 21, 1976 at about 11 a.m. Chicago time FDA inspectors telephoned Syntex from IBT. IBT had tried (supposedly unsuccessfully) earlier that day to make contact with Syntex to obtain their permission for FDA inspectors to examine the rat study data. The inspectors requested permission to audit the data which was readily given and the inspectors requested that the same be communicated to the IBT official in charge, Mr. Roman. IBT had maintained that they could not permit FDA examination of data without Syntex's permission due to contractual agreements.

Following the FDA inspection Syntex scientists also visited IBT. It is assumed that the impetus was not the FDA inspection per se but the revelations at the July 19-20, 1976 "Kennedy Committee" hearings because elsewhere in this submission it is stated that Syntex examined the data starting July 20, 1976.

Page 3

6. Top. Syntex claims that they obtained additional information beyond that obtained by FDA. At a meeting August 11, 1976 Dr. Hill and FDA compared data available to each for review.

It was established that at that time the only difference related to food consumption data and calculations of diet. This material had been seen at the time of the inpsection June 24, 1976 and was not judged at that time to be critical for any validation of the study in question.

It should be established if Syntex received any further materials from IBT at that time to which we so far have had no access. For example, there is a claim of notebooks by the animal study technicians. At the time of the inspection these were never suggested as being in existence. Is this a fabrication that Syntex knows we cannot prove or disprove. As to the comment regarding the one-half day inspection, it must be said that the inspection team of Dale Stelter, Dr. A. Gross and Mr. M. Hein examined data for one-half day on June 21, 1976 but were prevented from doing so by IBT on June 22 and 23. Due to other commitments they spent only June 24 further examining the data. Due to the extent of the many discrepancies noted most of the then available data base was copied (xerographic copies) and one set left with the company while two others were retained by FDA. The analysis of one of these FDA sets by the Gross-Hein team in Rockville, MD took to August 10, 1976 and involved at least 1 1/2 man months of analysis by these trained reviewers.

7. Middle paragraph. Syntex performed extensive review and reconstruction July 20-August 18,1976 of the IBT data. From this it is clear that the impetus was the "Kennedy Committee" revelations. The August 5, 1976 letter to Dr. Anderson of Syntex gave a list of particulars of the findings by the reviewers. There is a claim that the "reconstruction" was hampered by a lack of the inspectors reports. This must be interpreted as the Gross-Hein review of August 10, 1976 and not the actual EIR by Dale Stelter. As mentioned earlier on August 11, 1976, Dr. Hill and Mr. Bourdakis met with FDA at Rockville. At that time the Gross-Hein review was requested but denied to Syntex. The methods of how our data analysis was conducted, a comparison of what FDA and Syntex had in terms of data, a citation of examples from the report all were given verbally to Dr. Hill. Verbally FDA was prepared to reply to any of the scientific aspects that had been raised in the August 5, 1976 letter. Thus, the claim that the reconstruction was without benefit of the review is unfair criticism. Withholding the actual document was a legal decision at that time pending resolution as to the need for any legal action against Syntex or IBT. FDA then stated that if they released the report it would also be available to everyone else under FOI.

8. Next paragraph. I did not attend the August 20, 1976 meeting. However, I was given the assignment to audit the Syntex reconstruction (See report dated August 30, 1976). The verbal and the written arguments obviously were inadequate to convince FDA that the need to issue an NOH no longer existed.

9. Last paragraph. Syntex initiated on August 31, 1976, a 800 rat 2 year study. As this was started even before the NOH issued it must be considered that Syntex realized that the arguments presented were inadquate to convince FDA. It is also an admission by Syntex that such a study was needed to substantiate safety of naproxen. As the study was in conformity with the suggestions for 50 rats/level/sex over two years made regarding carcinogenicity studies by FDA to interested members of industry, it must be assumed that this is not just a toxicity but also a carcinogenicity study. Would Syntex initiate such a large and expensive study if they were convinced that carcinogenicity had been adequately tested by other means?

Page 4

10. The September 28, 1976 communication containing most of the mutagenicity studies was received, but this did nothing to validate the IBT long term study, supply new information on long term toxicity and also was not accepted as a valid substitute for any long term carcinogenicity study. Thus the need for the issuance of the NOH was not overcome. Any arguments by mail regarding this study or other future short supplemental pieces would have only served to delay indefinitely the settlement of the matter.

11. Middle. October 15, 1976 the NOH was published. On October 18, 1976 specific information as to the statements which were alleged to be untrue along with the supporting documents, was requested by legal counsel of Syntex. It is claimed that FDA did not supply the data. The basic data collected from IBT was available to Syntex, the NOH was worded in great detail and by furnishing a record of meeting memos, reviews of submissions, certain telephone calls, etc., it supplied specifics of the allegations and the supporting proof. While counsel apparently was looking for an itemized list of the numerous discrepancies, inadequacies etc. to which specific answers could be given, FDA refused on the grounds that it had not had an opportunity to exhaustively uncover each and every one of the defects. Also, it would entail additional FDA labor which we did not have to commit.

12. Last paragraph (to end of page 6). To this reviewer these appear to be legal pleadings. Thus we are not prepared to answer them for lack of competence in that area.

Page 7

13. Here arguments are presented as to why the IBT study (and for that matter, any long term duration study, in animals designed to test toxicity is not material to the safety or potential carcinogenicity of a drug in man.

One may ask if this is true why did Syntex do the 22 months IBT study (and the rhesus and minipig studies) in the first place and now a much enlarged 2 year study? Obviously they know we would not approve an NDA for a long term administration drug without prolonged toxicity studies.

If one accepts the Syntex argument that long term administration studies in animals are not indicated, what reason is there for any one to do any long term administration animal studies? Of all drug classes the non-steroidal antiinflammatory agents are probably as diverse a group as any, based on chemical structural relationships. They are used extensively for several years by the patients and often in conjunction with other therapeutic regimen, particularly since this group of patients is often prone to multiple disease entities. As the NSAIDs are not just simple molecular modifications of already established drugs the need for basic toxicological information is paramount. The information regarding carcinogenicity is of equal importance as information on any chemical entity is in this regard also unknown until tested.

Drugs are tested in animals to demonstrate a margin of safety and a toxicologic profile. This takes several forms. One means is to administer considerably higher doses of drug to animals on a mg per kilogram or mg/square meter basis than is attempted in man. Usually at least a factor of 5 is desirable, if technically possible. Another mode of assuring a margin of safety is to at the same time also administer the agent for a period that is at least as long and preferably longer than the duration intended in man. In this the relatively shorter natural life span of laboratory animals compared to man is used to telescope a life time experience into a few years.

Animal studies permit the use of a captive group of patients contained in a fixed and controlled environment where all events scheduled can be performed according to plan. In patients such control is not possible as the population is highly variable, the environment largely uncontrolled, the observations are not possibly performed according to a precise schedule and moral and informed consent considerations are involved. In man also it is not possible generally

to obtain gross and histopathological information. Thus what are the benefits gained by studying man? The metabolism is likely to be more appropriate (however this may vary with varying populations), the drug is studied in a species of subjects which actually have the disease (there are few good animal model systems for many clinical conditions) and the patient may benefit while under study. On balance what really is needed is any information that will enable the physician to administer the drug to the appropriate patients in as safely a manner as can be devised and armed with all the information from both animal and clinical studies. Generally there is reasonably good correlation between the principal human and animal findings if both the basic and clinical scientists have done their work carefully. Due to the inability to generally program the experiment adequately and to control the numerous variables involved (age, sex, diet, extent of clinical condition, therapist opinion, genetics, locality, climate, etc., etc.) it is essential to use often very large numbers of patients for tests of safety and efficacy.

14. Top page 9. In recent times, i.e., the last 1-2 years, HFD-150 has requested that manufacturers planning to market NSAIDs supply carcinogenity studies before NDA approval. Such studies should contain as a minimum 50 animals/sex/level at the start and have the following duration:

Rats 2 years of drug administration - no further observation period.

Mice, at least 1 1/2 years of drug administration.

For use in monkeys and dogs there are carcinogenicity study examples available in the trials regarding the oral contraceptive agents where the duration has been 7 and 10 years.

Many companies have chosen to make such carcinogenicity studies combination toxicity-carcinogenicity studies. The principal differences are periodic monitoring of hematology, clinical chemistry and sometimes urinalysis for a toxicology study and the greater emphasis on regular palpation and monitoring for the development of tumors in carcinogenicity studies. The carcinogenicity studies employ more animals and the duration of observation may be longer. The drug administration, animal care, housing, gross and histological examinations are generally identical. All these can be

achieved in a well designed and executed combination study. Addition l subgroups are frequently employed to allow for interim sacrifices and specific tests. The currently ongoing Syntex 800 rat study appears to be such a combination study as it will last 2 years with proposed 12 and 18 months interim sacrifices of some rats.

For toxicity alone the FDA standards are probably in agreement with statement by Dr. D'Aquanno as quoted. That this is not a new policy can be seen from the 1974 date of publication. The statements have probably been enunciated earlier in speeches. (Note this is long before this NDA was approved).

15. The question as to whether 3-6 months toxicity studies are adequate can be argued depending on which camp one wants to believe. While the EEC may take this view, it has no binding on the FDA which makes its own standards of excellence. There is no reciprocity. This argument of course also applies to the comments by Dr. McCollister and Dr. Hennesey as well as the requirements set by other national regulatory bodies.

Page 11

16. Syntex study on miniature pigs is claimed to have had ophthalmology in the protocol. The jacket is not immediately available to check it (but the reivew makes no mention of ophthalmology). This study was done by IBT too. The rat study had ophthalmology in the protocol also but was not done. Findings in this regard may be infrequent and the sampling of eyes in the minipig study may not have detected any problem if this indeed was done as the number of animals in this study was small. Also, it is admitted that these changes are slow in being developed. The swine had a 1 year of drug administration and the monkeys (done by Hazelton Labs.) only 9 months.

Page 12

17. Note the listing here includes the 6 months rat toxicity done by IBT concurrently with the sutdy in question. The technical quality of this is probably no better. The minipig study also carried out by IBT, but at another facility, may also be of questionable technical quality. The 6 months study in mice was a Syntex study but was of marginal value as only 5 mice/sex/level were involved.

It seemed that in the rat 160 rat 22 months study the incidence of gastrointestinal lesions was somewhat lower than might be

expected for this type of drug. Dr. Donovan Gordon then of IBT after completion of the study examined selected autopsy remains from some 20 or so rats and thereupon confirmed the GI toxicity.

At the time of the inspection, the carcasses then still said to be in storage at IBT were not examined but the inspection team questioned if the GI tract had been opened at the time of the autopsy to find the potential lesions. It was even considered whether to place these under seal.

There is no argument against the findings summarized at the bottom of this page but the information does not answer the question what effect the presence of the drug induced lesions may have after long term administration (1-2 years) on other systems and the general well-being of the animals. The lesions are such that they may not induce immediate mortality.

Page 13

18. Re: the FDA lifetime study requirement. See also reply to item 13 above: "Drugs are tested..."

Guidelines are just "guidelines" and not regulations rigidly enforced in every case since such scientific considerations as feasibility and benefit versus risk must be weighed.

NDA 17-573 is Vanceril (Beclomethazone dipropionate) which was approved for chronic use. It had only 12 months of study in the dog and 6 months in rodents. This is a glucocorticoid intended for inhalation and the technical problems with animal inhalation studies must be considered here as must the inability of animals to survive chronic large doses of steroids. The chemical structure is similar to prednisone and other approved agents which are well defined in animal systems. It seems to be intended as a supplement with other corticoid therapy in severe asthmatics. Clinical information at approval was extensive as the agent was marketed in the UK since 1972. The agent is now in phase IV with additional animal and clinical studies in progress currently. NDA 17-573 was approved by Division HFD-150 in 1976 but thereafter transferred to Division HFD-160 (for monitoring by Dr. Lidd). NDA 17-442 is Minipress capsules by Pfizer Labs and contains Prazosin HCl. It had a 12 months study in beagles. It is a hypertensive agent.

17-463 is Motrin (Upjohn Co.) and is therapeutically similar to Naproxen. The study cited here had 30 rats/sex/level and was a 24 months study. There was only a control and a single therapeutic dose level of 180 mg/kg which was later reduced to 60 mg/kg due to incidence of toxicity. It should be noted that there were 30/sex/level here and only 20/sex/level in the IBT study. The survival at completion of the study was higher (there was only 1 rat at high dose in the IBT study out of 40 at the high dose). Study was in England (by Boots) and this may have been the reason that FDA has so far not validated the study the same way we validated the long term studies for the comparable Lilly drug (Nalfon) and the McNeill Labs drug (Tolectin). With Motrin there also are available 12 months studies (10/sex/level) in rats and rhesus monkey (3/sex/level) which were carried out by Upjohn themselves. There appears that there also is a mouse carcinogenicity or long term toxicity study done in England which is cited but for which Upjohn never has supplied any data. (Can FDA get some more information through the British Food and Drug Directorate on this?). 17-463 NDA approval was a responsibility of HFD-140 and it was then transferred about September 19, 1974 to HFD-150. The IND work-up on both Motrin and Naproxen was largely done in the Division of Metabolic and Endocrine drugs. They came to HFD-150 about July 1, 1974 with the reorganization at that time. NDAs for each of the NSAIDs in question (Motrin, Naproxen, Nalfon and Tolectin) had been initially submitted to HFD-140 and came to HFD-150 at that time or shortly thereafter.

Page 15

19. Here the argument is made that other shorter studies have revealed all the toxicity and that the IBT study only confirmed such findings. Therefore it is not material and not needed. It is quite possible that additional previous unknown observations could have been made in the long term study if the study had been endowed with an excellence capable of detecting them.

20. Testimonials by Willigan, Hodge, Robinson and Litchfield regarding the adequacy of the toxicity data without the 22 months study are probably without merit as:

    (a) They were probably paid employees of Syntex and thus biased.

    (b) They were probably chosen for their viewpoints which have been expounded previously.

(c) Any evaluation of adequacy must come from FDA employees or from consultants selected by them to aid them by virtue of their expertise not their publicly held views.

Page 16

21. Regarding the Human experience data I will defer to the medical reviewer of Naproxen, Dr. Norris. However a few comments are made as thought helpful.

Page 17

22. It needs to again be reiterated that any human trials are not exquisitely controllable as good quality animal studies. Without having a high level of control any toxicity may be missed entirely and not recognized due to the "white noise" from any uncontrolled factors. (Environment, heredity, uniformity within the test system etc.)

Page 18

23. Zbinden although now in academia must be recongized as a representative of the drug industry which naturally would not be in favor of more studies. Note his former long association with Hoffmann-LaRoche.

Page 19

24. It has been the policy of FDA to keep the guidelines purposely flexible so that they do not constitute a 'cookbook'. This is done to foster innovation, permit us to determine adequacy and because it is well known that each drug substance has special problems in which a rigid 'cookbook' would have to be modified (i.e., drugs given by unusual routes clinically (sublingual? intravaginally etc?). It should be remembered that a study with perhaps 1000 subjects (animal or man) poorly done may be of less value than a good study with just 100 subjects.

25. Page 19, last paragraph. We would suggest the number of short duration studies is not unusual for this type of drug and the number of intermediate duration studies and longer studies (6 months or more) also is comparable and may even be low when the three IBT studies are set aside due to questionable quality.

There is a claim made that there are numerous studies of other members of this chemical class. This reviewer interprets that to mean other members of the anti-inflammatory group but it could also be interpreted as other chemical entities which have chemically similar structures. The chemical structures of various other members of the anti-inflammatory group (indocin, phenyl butazone, nalfon, tolectin and motrin) are quite diverse and the complete biological profile of each it totally unknown until discovered by actual experiment with each agent. To do this ideally side by side experiments must be done under uniform experimental conditions. Thus FDA cannot accept the argument that clinical (and animal) studies of Motrin, Nalfon and Tolectin are in any way supportive of Naproxen. While there may be considerable experience with Naproxen clinically, the documentated well controlled clinical experience is the only basis for our judgment.

Page 20

26. Middle paragraph. There is a discussion of differences in metabolism rates of Naproxen with different species. On page 32 of the application for the hearing it is claimed that the toxicological profile is very similar between various species. I would like to suggest that the dis-. cussion is meaningless unless other factors are also considered such as conditions of use, doses and routes of administration. In the data of Table III to support the present argument tritium is the indicator agent. Without knowing site of ^{3}H labeling and considering the differential potential lability of the label in various species, the data is not too helpful. Presumably analysis was by ^{3}H activity which may have been residing in the parent molecule, a metabolite thereof or even just a split off fragment such as a methyl group. Comparisons based on pieces of data from one study with those of another study to make a point are risky in that different methodological procedures etc. are used.

27. Lowest paragraph. The class labeling concept can only be established if the indication, effectiveness, safety, methods of use etc. are common. Special directions for each agent must be added to the basic document to account for the peculiarities of the agent if existant, such as doses, must still be individualized. I would not consider a warning statement adapted from the package insert of one drug to that of another as class labeling. FDA insisted on the warning statement in the absence of adequate controlled contra-indicative data. If FDA can be convinced to the contrary we would surely be glad to permit its removal.

Page 22

28. It is claimed that there is a chemical relationship between various anti-inflammatory agents. Based on this, similar indications and toxicity in animals and man supposedly adequate support for Naproxen exists. Structures of agents cited are:

Page 30

39. Here it is argued that the shorter duration carcinogenicity studies (really mutagenicity tests) render the 22 months IBT study no longer esential as a carcinogenic test system. We have to admit that even if carefully carried out this 22 months study with but 20 rats/sex/level could at best signal only a potent carcinogen even if there had been good survival which is not usually the case with this class of drugs. FDA now and for several years have requested that 50 rats/sex/level be entered. With the high mortality rate due to the drug's activity with this type of agent this probably is somewhat low (in the Motrin study about 1/3 of the animals survived for the full two years with drug administration for 2 years). Possibly the entering number of animals should be higher so as to permit at least 25-30 survivors/sex/level.

Syntex does not make a claim that the IBT study was a carcinogenicity study. Syntex alleged conversations between Dr. D'Aguanno and Syntex in 1972 which are alluded to on page 30-31 in which they state they were advised no carcinogenicity studies were needed. We have not seen documentation

of this claim. We can then only state that the NDA is deficient for lack of a suitable chronic toxicity study not both a chronic toxicity and a carcinogenicity study.

30. The middle paragraph quotes (incorrectly and out of context) a statement by reviewer Hein in his August 30, 1976 review (refer to item 8 page 2 of that review). The statement is a description of what the reivewers concept is of an ideal good long term toxicity study. Note the use of "adequate sample of animals" and "and to suggest that a low carcinogenicity potential exists which would obviate the need for additional specialized long term carcinogenicity studies." There is no statement to imply that the IBT study in any way met the criteria set forth and that carcinogenicity was of no concern.

Page 30-1

31. The conversation alluded to here in June 1972 is not documented. Suggest Dr. D'Aguanno reply to this.

Page 31

32. Reference is made to a quote by Dr. D'Aguanno in 1974- see item 14) last paragraph. In the absence of specific guidelines on carcinogenicity FDA has usually employed long term administration (over a major portion of the animals lifetime ") in an adequate number of animals. This can for economic reasons only be practically achieved in rodents (mice and rats) and also with larger species would entail far more prolonged study.

Page 32

33. Expert opinions again by Hodge, Robinson and Willigan - see answer to item 20.

Page 33

34. From the recommendations given out on NSAIDs in the past FDA must be in agreement with reference number 6 (NCI guidelines for carcinogenic Bioassay in small rodents) but due to the high mortality with this type of agent we suggest reference 4 being more extensive would be better.

Page 34

35. The carcinogenicity test has evolved in recent years and become a major factor in developing a safety profile for

any drug. Our recommendations in 1969 when the IBT study was initiated would be less severe than any given out today. Regarding the statistical suppositions we must defer to others with more statistical expertise. As of today we have no better test system that tests carcinogenicity in mammals and that is mainly why it is used.

Page 36 etc.

36. The "B. Ames tests" in selected bacterial strains are tests for mutagenicity and while somewhat crude have been accepted as a rough screen for this purpose. They are rarely used alone but usually in conjunction with other tests such as the "dominant lethal tests" and other newer "quickie" tests. It is argued that carcinogenicity implies that a cellular mutation has occurred and therefore the mutagenicity tests are also carcinogenicity tests. Due to the relative simplicity in carrying out, low cost and rapidity in terms of time in which an answer may be obtained they have often been advocated to help in establishing if an agent has a carcinogenic potential but they are not universally accepted as a replacement for classical studies and have never been so at FDA. The metabolism of a bacterium just cannot compare with that of a complete mammalian organism.

For such a vital parameter as carcinogenicity - which cannot be detected in man for perhaps 20 years of drug use and then only with sophisticated analysis of a superb body of clinical data - it is important to use all available tools and the Ames and classic tests are just two exmaples thereof. The acceptability of other tests in lieu of the classic tests is a policy matter.

Page 40-1 Comments on expert opinions - see item 20

37. Middle paragraph on page 45. Retention of raw data records. There is no regulation on a requirement to maintain these, but it should always be FDA's prerogative at any time to challenge the validity of the study which can only be satisfied by availability of the raw data. If the data did actually disappear this did not occur probably with the approval of the NDA, but earlier. Why was it so selectively lost? Why not all the urinalysis and weight records? Why only some of the autopsy sheets?

IBT may not have been inspected in relation with a drug substance until 1976 but has probably been the subject of an audit by other FDA staffers in the process of verifying some of the contractural work that IBT did in the past for the Bureau of Foods.

19

Page 46

38. The IND submission was in 1972. The very same and unaltered study was resubmitted in 1974 as part of the NDA. If the raw data was absent since 1972 then FDA could claim that the 1974 submission was made also with the absence of supporting data (at least partly unsupported by raw data).

39. The protocol provided for the generation of daily observations. By their own admission there was no observation on weekends. Under the term observations any reviewing pharmacologist would understand observation as to live/dead status and circling but also such notes as to fur condition, animal activity, color of unfurred parts, presence of diarrhea, response to handling, status of food and water supply, shivering or lethargy, etc. etc. It is inconveivable that these notations were ever made on cage cards especially if they also, in some cases, had room for autopsy findings. They were demonstrated to us at the inspection as being estimated at about 1 1/2 x 5 inches. In any case, this cannot be verified as they do not exist according to Mr. Happ at this time. The only place that we have seen any transcription or original entry of this type of information has been in the 32 weight records and here it was limited to a specific period when there probably was a specific caretaker in charge of this project.

    The protocol did not imply that there would be a daily check for tumors and the NOH in no way implies that there should have been.

40. The individual records for hematology and clinical chemistry are said to have been available in the 1972 report. This however was limited to just 5 animals (where available) per group. There is no way to determine on what basis these rats were selected or whether the values reported were selected from out of all the animals available. Even though here rat identifications are given, FDA has not so far tried to correlate these values with other findings (as we are not sure of the identity problem). For the final urinalysis there is no raw data and the individual values cannot be reconstructed as only a mean value is available at this time. Urinalyses have not been a requirement for long term rodent toxicity studies. This is usually obtained in larger species. The reported urinalysis determinations on rats are relatively meaningless for purposes of correlation with other findings as the mean is composed of different animals at different times in the experiment,

there is no range or standard error given and even in the raw data available at IBT in 1976 there is no specific identity to the rats employed (just #1 through 10 in each group without identity as to real animal #).

41. It is argued that the fact that some records were not saved is not crucial to the experiment. It is surprising that some records survived and others did not. Why were not all records destroyed? Especially since there was supposed to be no requirement to save all the records in the protocol and presumably not provided for in the intercompany agreement. The fact that Syntex did not provide for a mechanism by which all records would be saved either at IBT or at Syntex is of no concern to FDA.

42. Bottom paragraph. FDA and Syntex claim to have about the same data, i.e., 32 records of weight observations. We did not find any weight data records for the first 8 weeks of the study. The NOH answer claims that there were weighings 1-4 times at 1, 2, 3, 5, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, and 21 months. Besides attributing weighing(s) to the first month there is an admission that there were none for months 6-9 (we call it" from the 6th to the 10th month.)

Page 48

43. FDA cannot accept any interpolated values for any missing data whether this was done originally by ITB as may have been the case or now by Syntex in 1976. Not only is Syntex trying to justify the study on 32 weight data sheets but also now wants to make allowances for those on 1/20/70 and 1/30/70 which were "inadvertantly" recorded for the wrong period in time.

44. Middle paragraph. The physical impossibility to record adequately all gross and in vivo observations on cage cards has been previously discussed. (See 39). We have no argument with the accuracy of the transcriptions by Marilyn H. Biederer from the Histo-path logistics sheets but find that many are missing (about 86 from 116 for those animals that died prior to study termination). We have no way to check the transcription job for the records not available whether the information came from the sheets and/or the cage cards. That such information was ever recorded on the cage cards could not be established at the time of the inspection. There were also specific findings in the "Plank Summary" that were not contained in the log sheets or the Histopathology records. The inspectors have always questioned the source of that information and were told that this came from cage cards. If so, then this was not recorded by Marilyn Biederer to her log sheets.

Pages 50-53

45. The protocol specified the various tissues to be examined. Our findings of missing tissues induced IBT to imbed, cut, stain and examine in 1976 some additional tissues. Why would they do this if the information was originally available? There is no information regarding the accuracy of identity on this material or the condition of the tissues so that the procedure is technically not faultable. Where these tissues accurately marked while in storage? These 63 tissues cannot be admitted as uncontested additional evidence for this reason. (Dr. Gross's report will supplement this section). The incidence rate of tumors in these 63 tissues is higher than in the original tissues. Pooling the data, there still is no statistical significance to the incidence of tumors between the various groups. It may be possible that in these 63 the examination was more meticulous and more lesions were found than in the original sections. While tumors found in histology, but not in gross examinations are possible, too many of these would tend to cast a suspicion on the quality of the gross autopsy. If the "Tumors" detected on gross autopsy cannot be confirmed in histology it is possible that this is due to poor sectioning techniques in that the "tumor" was not available for the histologist to examine. (Accidentally or on purpose). With no pathologist present during autopsy and sectioning and with possibly inexperienced technicians doing the job (at least at some times during the experiment) at IBT these considerations must be entertained.

Pages 56-6

46. Here the quality of histological examinations after autolysis has taken place is discussed. Despite strong protestations to the contrary by Syntex (and IBT) in 1976 FDA has to assume that "NTT-no tissue taken" and "TDA Technician destroyed animal" mean just that. These definitions were supplied to the inspectors by Mr. Plank at the time of the FDA inspection and now there seems to be a trend to change this meaning. The degree of autolysis was graded in some animals on the log sheets by an arbitrary scale from 0 to 4. Regarding the ability to do good histological examinations on autolysed animals I must defer to more qualified professionals. Autolysis will discolor tissues and I question the ability of the technician to detect whether a color change is due to autolysis or to drug induced factors prior to death. The capability of the technician to autopsy the rats himself (as discussed in the middle of page 55) is questioned as he

did this probably with inadequate training and experience and no supervision. Also, he is unable to do this in a manner identical to that of the histo-path dept. (or necropsy dept.) because he probably does not have the same equipment, i.e., check sheets, light, tools, specimen jars, sink for tissue washing etc. Thus, there are "autopsies" of varying excellence and extent. Presumably the tissues saved for histological examination from a "necropsy dept. autopsy" and a "technician autopsy" was not the same.

Such further subgroups from the whole population (especially since there are only 20 rats per sex per level in total) reduced the reliability of the data to such a low level that no statistical inferences are possible.

Page 56

47. Middle paragraph. Here it is charged that the original reviewer (this would be in 1972 when study was submitted to the IND) and probably also the second reviewer when the same study was again presented to the NDA in 1974, was aware of the discrepancies and had drawn the conclusion that the histologic examination was adequate for the purpose of the study. Dr. Hsia and later Dr. Burns did pass the study. Dr. Hsia was undoubtably more concerned with the scientific evaluation of the study than an examination for technical quality and completeness. Dr. Burns, as is common in many such cases, probably did not rereview the study from the beginning but acted on the basis of Dr. Hsia's review. If indeed Dr. Hill of Syntex, according to conversations he had with Dr. Gross, advised FDA about his misgivings regarding this study it seems these reviewers were unaware of them.

Page 57-8

48. Here the quote is made form the NOH relating to the rat identity problem and the discrepancies in data. FDA is (again) accused of not supplying a specific list of the numerous inconsistancies. (See 11)). We cannot accept the reconstruction by Syntex (even if later agreed to by IBT as it is claimed) based on supposition, hypothesis, plausability likelihood, possibility, suggestion, etc. There are numerous instances where these cannot be "explained" and even if likely proven. Thus, FDA maintains that untrue statements of fact exist. We did not accept the August 20, 1976 reconstruction and the present effort is not materially different to a significant extent and must be denied for the same reasons.

Page 59

49. IBT claims there have been no transfers (mixups) between treatment groups even if there were some within the groups. It is only necessary to refer to animal #21 where it was left finally to the histological examination to determine that #21 (this number refers to a control female) had male sex organs. Except for sex identification it is not possible to prove in this study that intergroup mixups had or had not occurred and IBT probably is aware of this. (In some other studies the drug blood levels are taken that might serve as a clue; in others there may be marked differences between groups due to behavior, clinical chemistry, hematology, weight, etc. that could be a clue as to potential mixups provided the study has a good level of technical excellence.)

50. Lower paragraph. Is Syntex trying to imply that the weight loss always preceded death? That an animal about to die will naturally have a lower weight than a healthy one? If so, this is an important finding not previously reported in the IBT study and not established from other studies submitted by Syntex in support of safety on this drug. This would support the FDA contention that a long term toxicity study can generate data not available from short term studies. If, as described on page 60, there are such marked differences in weight within control animals treated alike for 3 months in a supposedly very carefully controlled study (the new 800 rat study by Syntex initiated September 1976) this is very unusual. As the circumstances at IBT and Syntex are not the same this cannot be a valid argument to excuse the variation in the IBT study data. An admission of differences of ± 200 g in male control animals 3 months into the study may even be cause to suspect the new study for quality.

Page 60

51. Second paragraph. Here FDA is asked to ignore the May 24, 1971 weighing and to reduce the total available information of raw data weight records from 32/100 to 31/100 (or is it 29/100 in view of the uncertainty of the 8-10 week records?). It is claimed that changes in weight of 10 grams per day are not unusual (See their footnote) for this type of study. This probably can easily be refuted by reference to any number of good quality studies, especially if this 10g/day change is cummulative and progressive over an extended period of time as with some animals in the IBT study.

For the opinions of experts offered, see earlier remarks.

Page 60-61

52. Tests of GI ulcerations in vivo are not possible in animals as small as rats but have been done by some investigators in dogs and humans. The rate of incidence of GI ulcerations in relation to time of death would be a useful analysis if the data available made this possible. If this type of lesion is suspected from drug action, would not monitoring the incidence of blood in the fecal material and relating it to animal unthriftiness and death be a useful substitute? (A necessary parameter to the study?) Knowing that GI ulcerations are a problem with this type of drug why did Syntex not provide for such analysis for fecal blood?

Page 61

53. Lower paragraph. The latest "reconstitution" by Syntex is claimed to be identical to that of August 20, 1976 except for additional previously unexamined tissues. If FDA found the reconstruction unacceptable on August 20, 1976 because Syntex made it rather than the individuals who actually did the study, this still applies in the latest effort. As indicated we have no proof of identity of the new tissues which are at least as dubious as those previously examined. The "explanations" with the reconstruction have been edited but that will not change the material facts.

Page 62

54. Second paragraph etc. Expert opinions...see 20) also see section A-1)

55. Arguments on page 63 have been previously addressed also.

Page 64-6 Section IV is a recap and summary of the previous points addressed.

Page 67 Section V

57. This is a request that FDA delay, pending completion of the ongoing studies, any final decision on Naproxen. This study that was started in September 1976 on 800 rats cannot be complete in its "active" phase till September 1978 and when the data analysis, pathological examination, statistical measurements, actual writing of the report etc. are also considered this cannot be made available to FDA for review at its earliest even with the superior manpower available

to Syntex (the reconstruction effort was accomplished from July 20 to August 20, 1976) by at least January 1, 1979 and probably later. Is FDA to allow Naproxen to remain on the market till mid-1979 with the questions of long term toxicity and carcinogenicity unanswered? If the IBT study is immaterial to Naproxen safety evaluation, then the 800 rat study is also immaterial. If the new study is material (why else do it?) FDA ought to await the outcome of the results before we allow Naproxen to be used over extended periods of time. (Therefore remove it from the market until the study in question is completed, submitted, properly verified against the raw data and evaluated.) By 1979 it can be forecast the argument will be, should the animal studies prove to be adverse, "We now have 7 or more years of clinical experience". This is not enough to make sure that the drug has no carcinogenicity. To determine this from clinical studies alone the groundwork needs to be laid now that the patients can be followed and the incidence of cancer measured against a control population. FDA will need rates of incidence in relation to dose, length of use, possible interaction with other agents, employ environmental considerations all in a well defined population. Is Syntex able to do this? The 800 rat study is programmed for 12 months and 18 months interim sacrifices. Will attempts be made to clear Naproxen after each of these benchmarks?

Manfred M. Hein

Manfred M. Hein, Pharmacologist

JAN 14 1977

COMMENTS REGARDING STATEMENTS MADE IN VOLUME 3 (EXHIBIT II - SYNTEX RECONSTRUCTION OF THE IBT RAT STUDY)

This volume of about 464 pages contains an annotated version of the original approximately 59 page IBT report, the "J. Plank Appendix" to the report and Syntex's reconstruction of each section of the original report as deemed applicable by Syntex.

(The pages are numbered consecutively at the bottom of the page and this I.D. is used in these comments).

A. Regarding the Introduction Section:

1. Page 1. It is claimed that at the time of the writing of the report by IBT to Syntex in December 1971 and January 1972 (??) there was available to IBT considerably more raw data which has since disappeared. There is no mention that the report dated January 4, 1972 from IBT to Syntex is really the second effort. The initial report of about November 1971 from IBT to Syntex had been rejected. It, therefore, is likely that if any data was actually destroyed this occurred about October-November of 1971 at the time of preparation of the original report. It has not been possible to establish with certainty that the missing data actually ever existed (or did not exist) for this study. The "possibility" that some data points were actually "borrowed" from another study (i.e., the 6 months study that IBT did for Syntex on the same drug about the same time) has not been examined. It seems that the Syntex reconstruction effort was performed largely by Syntex scientists and later agreed to by IBT employees. FDA was told in a November 1976 meeting between the Bureau of Drugs and IBT that IBT had had an active part in the effort (a joint reconstruction effort).

2. Bottom page 1. The claim is made that the cages for the animals were identified by color coded cage cards listing animal number, dose level, sex and study number. The inspectors saw some cage cards at the time of the inspection in June 1976 and at that time they appeared to be about half the size of a library card (half of a 3x5 card). They were color coded but we did not establish at that time that they were coded as to study/or/sex/or/dose level or something else. The writing on them listing the study and animal number and sex was made by black marking pen and filled most of one side of the cards. It is alleged that behavioral characterisitics and other in life observations (e.g., "tumors" "pneumonia") were entered on these cards. At the time of sacrifice it is claimed gross mortem observations and cause of death determinations were entered to the back of

of the card by animal room technicians or in the necropsy area. I want to suggest that the size of the cards in use at IBT were not of sufficient size to do this job adequately, may have been replaced periodically (were they in use for up to 2 years each?) and so did not carry a complete record of in-vivo observations till transfer at time of necropsy to another log. They required removal from the cage before they were written on and so presented a potential source for misidentification between animal and the recording card.

3. Records relating to diet preparation. Food consumption records were maintained for the most part of the study on 5 animals/sex/level. There is no way to determine which animals were used (the same each time from those remaining of the 20/group?). The records are not complete. (The situation is apprently analagous to urinalysis problem).

4. Page 2, middle of page. "Study book". A separate study book was maintained by each technician it is claimed for each study which contained in life observations and weights. At the time of our inspection we asked about such additional data and the existance of such notebooks was never claimed. It is noted that loose data sheets were saved but not presumably hard cover and possibly bound notebooks. Recent IBT studies use ledger type notebooks which we were shown during the inspection in June 1976.

5. Page 2. Body weight sheets. Here it is claimed that there were weekly weighings which were entered in the study book. If this book was not available they were recorded on sheets and then transcribed to the study book. Apparently the main study book was not available on 32 out of 100 occasions for the recording of data. If indeed the data was transcribed from sheets to the study book we have no way to determine if the transcription was accurate as the study books were not seen by anyone (including Syntex) who tried to validate the study. Reference is made to the recording of clinical observations on such sheets also when they were in use. The Gross-Hein review team found very limited information entries at only selected times of the study on such sheets. If this was the normal practice why were notes to this regard made on cage cards?

6. Page 2. Re: Mortality log. "The technician would go through the animal room daily, except weekends (our underlining), looking for dead animals." This is an admission that animals were not even checked once on weekends which may

have lasted 2-3 days. Thus they could have been for that time without water." If any dead animals were found, an entry was made by the technician on the mortality log which was kept in the animal room." As the Necropsy log (the "Marilyn Log") was kept at Marilyn Biederer's desk and not in the animal room we now here learn of another record that has previously never been admitted to and is not the same as the necropsy log. The FDA investigation team has never seen a single copy of this mortality log if it differs from the "Marilyn log". (Is this the explanation possibly for the existence of several versions of the "Marilyn Log"?) As the animal caretaker handwriting would likely be different from that of Marilyn H. Biedeer this too is unlikely.)

7. Page 3. Animal disposition records. As each animal was sacrificed or died an entry was made in the animal disposition record with a separate page for each treatment group, i.e., a page for each of the 8 treatment groups within the study. Such a record also has never been available at the time of the inspection and may be another case where its existance is hard to establish 6 years later.

8. Page 3. Gross pathology sheets. FDA is told that during the time of the Syntex study there was a changeover from recording the gross observations noted at autopsy from cage cards to a primary recording onto histopathology sheets. Examination of the histopathology sheets available (some 40 out of an approximately total of 118 that should have been prepared for animals that died prior to the completion of the study) will reveal that they were prepared at all times during the study and not just at the end which would indicate that there was a change in the procedure.

9. Page 3-4. Re: Histo-Path sheets. "During the study, a chronological list was kept of all animals dying during the study". We have nicknamed this the "Marilyn Log". It is also referred to as a necropsy log. There are more than one version of this in existence on this study. The information was said to have been transcribed from both cage cards and the histopathology log sheets but that does not mean that there were no errors in transcription from the cage cards. In the case where histo-path sheets existed there were no additional entries which came from the cage cards (for that specific animal). It is alleged that there were 6 copies of this lot at time of study completion with three going to the wet cutting, embedding and sectioning

departments, one copy to the pathologist and one being retained in the necropsy lab. "Pathologist" here must be inferred to mean the IBT supervising pathologist as the consulting pathologist (Dr. Richter) received a different form with the slides at the time he examined them. A sixth copy was sent to the animal department. If the distribution was made only after the completion of the study it is impossible to see how it would have been of use to the animal department and the various sections of the histology section since the animals with death prior to completion of the study were processed without benefit of the log.

10. Page 4. Animal list for the Pathologist. When the slides were sent to the consulting pathologist (Dr. Richter) a separate log was prepared listing all the gross findings noted and other identifying information. It was our impression that Dr. Richter never saw the Necropsy log (Marilyn Log).

11. Page 4. Histopath report. When the pathologist read the slides he is said to have recorded his findings on the Histo-path reports. We did not find any entries by Dr. Richter in the sheets noted under 8. above. What is meant here is that the pathologist made entries in the log sheets prepared for him. He is claimed to have noted only positive findings by organ and animal. Unavailability of a slide was to be noted by a "dash". If the space was blank then the tissue was judged as normal. Syntex also prepared in 1976 for FDA a list of all the tissue slides that were turned over to them by IBT. We understand these to be the same as seen by Dr. Richter. There are some discrepancies between the Syntex list and the report that Dr. Richter submitted to IBT if one assumes the system of notation indicated.

12. Page 5. Pathology sheets. This particular set the inspection team has termed the "Plank Report" and is supposed to be a pulling together of all the gross and histological findings on each animal where available. It is an appendix to the report submitted in 1972 to the IND. Syntex now claims it to be just an information report that was intended as a part of the NDA. Here only positive findings were noted and missing slide tissue preparations were not noted. It is claimed that some of the information came from the cage cards, the histo-path sheets, the study books, animal disposition records, the pathologist report and the necropsy log. It should be noted that the age of the animals' death was not always in agreement with other records. Thus the validity of other transcribed data is naturally also subject to question.

13. Page 5. Urinalysis data. In examining this section of data one needs to know that there were no raw data records for the final urinalysis test point and that the animals chosen for this testing at each time point were randomly selected from the animals available in each test group. The protocol specified 5 but 10 were actually done (when available). The data is not useful to follow the progress of an animal as the data sheets are numbered 1-10 for each test group rather than with the actual animal number (i.e., 3, 7, 11, 15, 16, 17, etc. for control males). This also makes correlation with histological findings an impossibility.

14. Page 5. Organ weight raw data. At final sacrifice and not on animals that died during the conduct of the study, individual organs were weighed and recorded by animal number. In the initial set of raw data animals were entered as sacrificed. This sheet included the pituitary weights. A second copy was then made which listed the animals sorted into the treatment groups. This did not contain the pituitary weights and was used for entering the data into the computer. We did not note significant transcription errors otherwise.

15. Page 6. Preparation of the Original Report by IBT. This is really the second report. It is claimed to have been drafted in January of 1972 yet was submitted by IBT to Syntex under the dateline of January 4, 1972. All of the above data supposedly was available to the drafters of the report. So far we have no proof that this was all available in November 1971 or when the January 4, 1972 report was prepared. At the time of the inspection we were informed that Mr. J. Plank was the study monitor and also the person that wrote much of the report. The "sign-off sheet" on the report also contains for report preparation: Philip S. Smith, B.S. (no longer at IBT); for report approval: the names of Plank, Paul L. Wright (no longer at IBT) and M.L. Keplinger Ph.D. (who at the time of the inspection was not available for interview). The pathology data was certified by Drs. Richter and Dr. Donovan G. Gordon, D.V.M.

The data collected at final sacrifice, i.e., the hematology, blood chemistry and final urinalysis data was said to have been directly transcribed into the report without use of any raw data sheets. (This is very peculiar as means are given and the computation of same must have involved at least a listing of numbers, their addition and subsequent division by the number of observations.)

It is again noted that there is no proof that any gross observations were ever noted on cage cards. The examination without use of a running check list would be less than adequate when performed by the animal caretaker. In this context we are now told that the gross findings from the cage cards were used to make up the histo-path sheets. Elsewhere, we are told that they were used in lieu of cage cards for autopsies and that the procedure was in the process of change-over at the time of this study. Which is correct?

"For all but the TBD/TDA animals, the cage cards recordings were also transcribed to the necropsy log" (Also the NIT group?) If they were actually examined and records made why was the data not transferred to the necropsy log?

The microscopic findings were recorded by Drs. Richter and Gordon directly in the histo-path sheets. Dr. Richter did make notes on the log forms prepared for him and not the histo-path sheets described under 8. Dr. Gordon was not the regular pathologist on most of the tissues and only looked at selected animals that died during the course of the study and had been preserved in storage. His observations were limited to certain tissues and not an overall examination of tissues from an animal or group of animals. The original IBT report stated that Dr. Richter looked at the animals that died terminally and Dr. Gordon at those that died during the course of the study. It is unlikely that Dr. Gordon looked at many of the animals that died during the study as he joined the IBT company only in September 1971 and was not there during the major part of the study and surely provisions for the examination of tissues from animals dying prior to completion of study would have been decided before he came. It is claimed that the tumor table did not include any unconfirmed tumors, e.g., only those histologically verified. I like to suggest that with the tissue collection and autopsy procedures prevailing it is quite possible that the "tumor" tissue noted at autopsy or in vivo was not made available to the histologist for examination.

16. Page 7. Syntex reconstruction. Much of the comments that need to be made in this regard have also been made already in the August 30, 1976 review of the "reconstruction" and in remarks set forth in the first part of this review. Comments will therefore be only in relation to some new or newly found points.

On page 8, lower paragraph. It is now stated that "Regarding ophthalmology, it is clear from the NDA that no ophthalmology

or slit lamp examinations were done, and none were reported in the original report. A number of eyes and optic nerves were, however, examined histologically." In the protocol submitted with the IBT report to the NDA under clinical observations there is the following:

"4. ophthalmology-day-7, 3 months, 9 months, 12 months, and 18 months"
"5. At termination carry out slit lamp examination of 5 males and 5 females of each group."

The submission of the uncorrected protocol would lead the reviewer to be informed that the procedures were done and the data should be part of the report. It is correct that no mention is made of this in the original IBT report but the protocol also differed in other respects from the report i.e., number of animals (this is accounted for by the 6 months part of the study), housing animals individually, daily observations of general condition and behavior, there should have been an appendix for maintaining the animals over and above 18 months (22 months), reports of individual (not just mean) body weights, statistical evaluations of some parameters, direction to pay specific attention to the entire length of the GI tract, quarterly reports which should contain a minimum of data etc.

This reconstruction is essentially identical to that of August 20, 1976 except for the addition of some tissues that were imbedded, sliced, mounted and examined from those that had been in storage. Dr. Richter, the principal histopathologist on this study examined these also. Although additional tumors were found, the overall incidence of tumors does not permit a statistical finding that related drug dosage administration to tumor incidence.

Manfred M. Hein

JAN 14 1977

COMMENTS REGARDING STATEMENTS MADE IN VOLUME 6

This volume is in two parts; one covering the IBT autolysis study which was previously submitted by IBT in November 1976 and which requires a pathologist to fully comment on; the other is entitled:

Exhibit IV Naproxen Analysis for Potential Toxicity

1. Page 1

   It is here stated that "...the rodent test may no longer be adequate as the sole (our underlining) means of gauging carcinogenic hazard..." In an area where the ability to predict from animal and in vitro studies is less than perfect I would concur in that all means to arrive at a predictor should be used and thus the (long term administration) rodent test should not be considered as the sole means at assessing the potential for carcinogenic hazard.

   Regarding the statistical speculations, I can only suggest that if the extrapolation is as stated the need to do the animal tests as meticulously as humanly possible is imperative and the need for larger numbers (i.e., 50 or more/sex/level) is more than amply justified, especially with the larger than usual dropout rate (early deaths before completion of study) seen with this type of drug in animal studies.

2. Top of page 2

   The detection rate of cancer in rodents is potentially 100% if the autopsy and histological analysis is carefully done. In man the detection rate is probably considerably lower (how many as yet clinically not significant prostate cancers are detected in man on autopsy?). The relationship of tumorgenic incidence in rodents to a specific chemical is usually clear, but in man this can be almost completely obscured by uncontrolled environmental and other factors. It is the universal ability to detect tumors at autopsy in animals that gives us far better data from this source than man can supply as only a selected few humans come to autopsy.

3. FDA would concur that the "short term" tests discussed are good pre-screening tests and as such the best available today but these universally lack the ability to test the agent in a complete mammalian system in which metabolism, cell reproduction, cell specialization and modification of the cellular environment by other specialized cells of the same organism (i.e., hormones) is very much unlike that of bacterial and yeast systems.

4. Top of page 3

"All carcinogens which act directly on DNA are mutagens but not all mutagens are carcinogens." There are some chemicals that may induce carcinogenesis by attacking the RNA systems. Chloroform is considered a carcinogen, however, we are under the impression that it was not detected as a mutagen in the B. Ames tests.

It is here also argued that mutagenicity is most sensitively determined using bacterial systems. The reasons are not stated but are obviously the large number of "subjects" that can be studied and the rapidity in which the studies can be done due to the rapid bacterial (and yeast) generation times. Since genetically large numbers of alike "subjects" are available it further is possible to set up all the needed control groups which receive the vehicle only, a positive control, various concentrations of the tests material etc.

Some chemicals have been argued to require liver activation, but the potentiality that other chemicals require activation which normally takes place in portions of the gastrointestinal tract, in the kidney, blood or elsewhere does not seem to be considered. Use of a complete mammalian system obviates the need to locate the potential activating organ.

5. Bottom of page 3

Naproxen is strongly claimed not to be a mutagen and thus cannot be a carcinogen. Without a test in a complete mammalian system i.e., a long term toxicity study (24 months in the rat and/or 18 plus months in the mouse) using an adequate number of animals FDA cannot accept this proposition.

6. Page 4

This speaks to the applicability of the "B. Ames tests". (Tables II and III list chemicals that have been tested. This is a list from the literature without making any claim to being a complete registry of all chemicals tested in this way. It probably is however, a selective list in that many drug substances for proprietary reasons are not listed. It would be useful to have someone identify each of the chemicals listed also by the respective generic (and/or trade name). The column identified as "carcinogenicity" in Table III is not identified as to what constitutes a conclusion of a positive finding. Animal long term administration studies, human findings or both? I have not tried to locate the complete reference but this may explain this.

7. Page 5-7

Naproxen is concluded to be non-mutagenic and so non-carcinogenic based on:

a. Chemical structural analysis of Naproxen and its principal metabolite. There is no mention of all the potential mateabolites in man. There further is no mention as to what Syntex would consider as "related chemicals" other than these constitute a group of "substituted naphthalene derivatives of a simple aliphatic acid and is acidic when in aqueous solution." We are being given to understand by one of our colleagues that the acetic acid derivative of naphthalene is a potent plant hormone in that it promotes root growth. It is further a skin irritant. Would this justify such an agent as a suspect carcinogen when introduced into mammalian systems?

b. Naproxen is claimed to contain no "active" "transferrable" aliphatic group. These terms active and transferrable are here used without definition as to biological or chemical activity. The principal metabolite is a demethylated compound. Thus a chemist would consider the methyl group "an active transferrable aliphatic group".

c. The residence time in the complete mammalian organism (preferably man) of the parent substance and that of each of the metabolites may be an important consideration. Is the metabolite as readily excreted? What are the binding characteristics to plasma proteins which can serve as a "slow release depot" for the chemical?

8. Page 8

Naproxen and its metabolite(s) are aromatic acids and conjugated aromatic acids. Does the daily repeated (or even several times/day as may be the case in clinical practice) exposure by aromatic acids induce irritation to the GI tract and other tissues that if prolonged induces hypertrophy and compensatory mechanisms which may be akin to beninh tumors? Can these later become malignant under the continued irritation?

9. Page 8 lower part

It is claimed that the aromatic carboxylic acids have been negative in the "Ames tests" including Ibuprofen, Tolmetin, Fenprofen and Indomethacin. In the appended tests by Litton Bionetics

performed just in the fall of 1976 Naproxen, the principal metabolite of Naproxen, Fenoprofen, Tolmetin, Ibuprofen and Indomethacin were tested. To us there seems to be at least marginal activity in some of these systems. In the D4 strain of saccaromyces cerevisiae without activation by liver homogenate RS 2883 (Indomethacin), RS 7321 (Ibuprofen), RS 81842 (Tolmetin), RS 81872 (Fenoprofen), and RS 3540 (Lot code C of Naproxen) seemed to show some activity over and above the solvent control. In the case of RS 2883 and RS 81842 this was demonstrated more than once. In the activated (liver homogenate) system, RS 7321 (Ibuprofen) showed some activity.

In the TA 1535, TA 1537, TA 1538, TA 98 and TA 100 systems without liver activation there were only rare isolated instances where the incidence exceeded the vehicle control. In the activated (liver homogenate added) systems using these tester strains rare incidences were noted where the incidence exceeded the solvent control. We believe these to be real findings as they usually occurred at the higher concentrations of the drug substance and then in more than one concentration for the particular system. Naproxen, Ibuprofen and Fenoprofen were also tested in the E. Coli system on November 24, 1976. At the higher concentrations (500 and 5000 micrograms) both in the unactivated and in the activated system some activity was demonstrated for Naproxen and Ibuprofen but not Fenoprofen.

Tests in the mouse lymphoma system with Naproxen, Fenoprofen and Ibuprofen also suggest mutant activity with Naproxen and Ibuprofen. The submission suggests that this is due to decreases in pH induced by added drug substance. The reduction in pH for Fenoprofen was also significant but did not show the same mutant effects.

We do not consider these findings as particularly alarming and feel that they show only a low level of activity which by some may be interpreted as no activity and others as marginal only. Dr. Busick of Litton Bionetics in his report ascribes no activity to any of the agents tested in any of the mentioned systems. He, however, notes:

> "all evaluation and interpretation of the data presented in this report (these reports) are based only on the demonstration of or lack of mutagenic activity. Implications of potential for carcinogenicity cannot be made without additional evaluation."

88-938 O - 77 - 15

10. Page 12

It is suggested that Fenoprofen was tested in the 18 months rat study and no carcinogenicity was found. (We now routinely ask for two years of study in the rat.)

We cannot agree that the CH_3-C H-COOH grouping is the only potentially active group in all of the agents belonging to this subgroup of NSAIDs and that the added part of the molecule is without activity (or modification of activity) in fact just extra molecular bulk. (If so, the toxicity profile would be identical and doses purely related to molecular weight).

11. Page 14 "Re: 5. Modified Dominant Lethal Assay"

Reference is made to Appendix I for this data but I was unable to locate it in the set of volumes presented to me for review.

12. Page 15

Reference is made to the mutagenic activity of mouse lymphoma cells when the pH is lowered, as when there is addition of drug. Fenoprofen also lowered the pH but did not seem to be active as an inducer of mutants. The data is not especially in support of the contention that there is no mutagenic activity. The submission informs us that this is very preliminary data and that the methods are not very well established and thus the material "cannot be interpreted".

Manfred M. Hein

Manfred M. Hein JAN 14 1977

MEMORANDUM

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

TO : Dr. Marion J. Finkel
Associate Director for New Drug Evaluation, HFD-100

DATE: January the 19th, 1977

FROM : M. Adrian Gross
Scientific Investigations Staff, HFD-108

SUBJECT: Review and Evaluation of the Syntex Submission in Response to our Notice for Opportunity of Hearing (NOH) to Withdraw the NDA on Naprosyn.

This memorandum is a follow-up to the one under reference which I wrote to you on January the 14th, 1976.

You may recall that, among other things, I drew attention there to certain false information submitted to the Government, and that I recommended that we give serious thought to prosecuting IBT and/or others for possible criminal violations of the law.

A possibly related matter just came to my attention and I wish to share it with you:-

The Syntex submission which was the object of my review is dated December 13th, 1976; at least this is the date appearing in the Required Statement presented on the page before last in Syntex' first volume.

At the bottom of page 458 of Exhibit II we read:- "Syntex has conducted a thorough review of all the histopathologists' notes and the NDA Pathology sheets, comparing them to items noted in FDA's letters to Syntex (dated August 5, 1976) and IBT (Dated September 29, 1976) and to Dr. Adrian Gross' review (dated August 30, 1976).* All but four tumors found in four animals were reported in the NDA...."

Syntex then lists the four animals with tumors not reported to the FDA:- Animals 21, 59, 77 and 100. Note these four numbers for later reference.

I am now reviewing the IBT response to Dr. Leventhal's letter to them of September 29th, 1976 - the response is dated November the 11th, 1976.

On page 90 there we find a statement signed by Dr. Richter where he says that on October 9th, 1976 he examined a number of "additional slides" from the rat study at issue here. He also states " There were an additional 9 tumors among 9 animals that were not previously reported." On page 95 there is a list of these animals:- 1, 12, 33, 60, 64, 61, 71, 93, and 102. Compare these numbers with those underlined above.

No additional comments by me seem necessary here.

MAG:-

MEMORANDUM

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

TO : Associate Director
for New Drug Evaluation

DATE: FEB 1 1977

FROM : M. Adrian Gross
Scientific Investigations Staff, HFD-108

SUBJECT: Syntex' Response to our NOH Regarding Withdrawal of Naprosyn NDA

The following are the comments requested by you today on the evaluations made by Syntex' "experts" Drs. Robinson, Williqan, and Hodge. For ease of presentation their points are summarized on the left and my reactions are listed on the right.

Dr. Harold Hodge - Syntex' Vol. 2, p. 41

p. 41 - Materials he examined are listed

he "examined only portions of the raw data".

As far as I am concerned it is the raw data which makes the study unacceptable.

p. 42, paragraph 2 - "The IBT study, despite its flaws..."
paragraph 3 - "Although there are problems with the IBT report..."

paragraph 4 - implication that a drug effect may have been present in the kidneys

not reported as such by IBT in original submission.

"The lack of sufficient histological material from the high (toxic) dose group is a serious deficiency and in the absence of other information would disqualify the study."

!!!!

p. 42, paragraph 5 - he gives his opinion that "the chronic toxicity of Naproxen has been reasonably adequately elucidated."

p. 43 - "The errors and omissions ...are not such as would require any changes in those conclusions."

Has he seen the Hein-Gross memo of 8/10/76 where we list the errors and omissions?

p. 43 - "a high incidence of tumors should have been discovered on gross autopsy examinations..."

What is "high"? 100%? 90%? What about an incidence that need not be "high" but is significantly in excess of that in control animals?

What assurance does Hodge have that the gross autopsy examinations were adequate? We certainly have ample reasons to doubt this.

p. 43 - "Because the number of animals utilized in the study was small it would not today be evaluated as a definitive carcinogenicity test."

Hodge's Appendix - page 73 - on IBT's report

point 9 - "it was difficult to ascertain how many rats in each group developed stomach lesions."

(!!!) This is the only drug-related lesion reported.

point 10 - "the records of tumor incidence were confused."

Amen

Hodge's - on Syntex reconstruction

9 separate points are given here which are all subjective "opinions" on the quality of Syntex' reconstruction.

Hodge's - (detailed comments on IBT's report)

This is mainly an evaluation of what is reported by IBT; it is not the source of difficulties we perceive with this study.

Hodge mentions some problems that he sees: - the "considerable" variation in food consumption in the first 13 weeks; he asks "are such differences frequently observed at the start of feeding rats in their laboratory"? "One sequence of food consumption data is unusual. In the control males at the ninth month the food consumption was 169g: in the 10th month - 188g, in the 11th month 187g

in the 12th month 165 g. i.e. differences of 20 g. in average food intake per week. Looking at the overall body weight picture (see figures) it seems peculiar that there were no significant differences in food intake."	I'D say that Hodge is getting here the picture we got.
	Hodge perceives some problems with the hematology data.
	He also questions some of the clinical chemistry data.
p.3, paragraph 4 - "Unfortunately, a substantial number, especially of male rats at each diet level when found dead were unsuitable for study; this was the case for nearly all the rats in the 30 mg/kg groups..."	This begins to sound close to what we have been saying.
p. 3, paragraph 5 "Deaths were attributed mostly to chronic respiratory disease..."	They were so attributed in the IBT report though not so in original observations.
p. 5 - bottom third Hodge notices discrepancies between individual animal tumor data and summaries of tumor incidence.	Similar to what we have noted.
p. 6 - table at top of page	From Hodge's table 2 animals with tumors of any kind amongst the 40 controls versus 7 animals with tumors of any kind amongst the 40 low-level animals would be borderline significant at p=0.077152
Text - Hodge notices no histological confirmation on several tumors noted grossly	Similar to what we have seen but not as detailed.

Hodge's Detailed Notes on the "Reconstruction"

p. 1, paragraph 1 - even with the "adjacent cage" theory unexplained weight changes remain	Similar to what we have been saying.
p. 1, paragraph 2 - "The raw data available had been recorded at intervals of 2 weeks rather than monthly after the first 13 weeks as the protocol provided."	This statement is simply not true both as to the intervals and the protocol requirements.

In general this entire discussion is on the evaluation of the data; this is not the principal problem here. Rather our difficulties are with what are the data?

Hodge's answer to Syntex' questions

Q. 1 "Since the mouse has a lifespan of 18-22 months and since both monkeys and miniswine live for many years, more of those studies (6 months mouse study, the 39 week monkey study and the 1 year miniswine study) fills the requirement of exposures over a substantial fraction of the life span."

This pretty much pulls the rug out from one of Syntex' prime arguments.

Q. 3 - Can all data give adequate evidence?

Hodge's answer here is that only "reasonable basis for evaluating the safety of RS3540."

To me this may not be the same as "adequate evidence."

Hodge also states here: "The absence of histopathologic data from the high level rat dose can be offset by the extensive human dose."

I see no basis for this statement particularly in light of what Hodge answered under Q. 1..

Q. 4 - What value has the IBT rat study as a carcinogenesis study?

Hodge's answer here is not an answer to this question.

Dr. Robinson's Communication - Starting on p. 138

paragraph, p. 139

Robinson refers to "certain deficiencies" in the rat study but he has reference only to the missing records and not to the myriad of other faults we have signalled.

paragraph 1, p. 140
"all but one of the 'pituitary adenomas' were observed microscopically...

Not true - see Hein-Gross memo of 8/10/76

paragraph 2, p. 140
"With respect to carcinogenicity, the IBT study, as designed, would have had little value, even if perfectly conducted and reported, and would have only detected a potent carcinogen."

I shall not dispute this.

In general Dr. Robinson gives only opinions in his 1½ page letter.

Dr. Willigan's Comments pp. 153-155

p. 153 - bottom paragraph
"...there are problems with the IBT study..."

There is no description or list of such problems.

p. 155, paragraph 2
"With regard to carcinogenicity, while there were not enough animals included in the ongoing 22-month study for an adequate classic carcinogenicity study, the study nonetheless would have picked up a potent carcinogen."

What about a carcinogen somewhat less than "potent"?

SUMMARY

Although Dr. Hodge appears to have given more thought and analysis to this task than Drs. Robinson and Willigan, it still seems to me that each of these three gentlemen made no more than a superficial examination of the raw data gathered from this study.

If they did more than this, they certainly do not reveal in detail what they found there in anything approaching the scope of what we have noted.

Their comments are concerned mainly with the analysis of the data and they are replete with opinions. It seems to me that none of the three is paying much attention to the central question here - what are the data? Rather they focus on such issues as what do the data reported by IBT (or "reconstructed" by Syntex) seem to say.

For this reason I believe none of their "opinions" are worth very much.

Still, it was interesting to see that none of them were impressed with the value of this study as a carcinogenesis trial aimed at detecting a carcinogen somewhat less than potent.

It was also revealing to read Dr. Hodge's impressions on the value of the other studies (mice, monkeys, miniswine) as far as assessing the long-term effects of Naprosyn.

M. Adrian Gross

MEMORANDUM

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

TO : Dr. Marion J. Finkel, HFD-100

DATE: February the 8th, 1977

FROM : M. Adrian Gross, HFD-108

SUBJECT: NOH to Withdraw Approval of NDA on Naprosyn (Syntex)

With reference to my memorandum to you of January the 14th on this subject, I would like to make a correction of an error which had crept in there:-

The footnote at the bottom of page 12 of that memorandum refers to 50 "final sacrifice" animals according to Tables XXIV - XXVII on pp. 47-51 of the IBT report.

The correct figure should be 44 rather than 50; this would then leave 160 - 44 = 116 animals having died during the study (rather than 160 - 50 = 110 as noted at the end of the same footnote).

Because of the same error, the line before last in paragraph 2 on page 12 of my memorandum to you should also be corrected by inserting the word "nearly" just before "one-half of all dead animals?*"

The fact that this error had occured is my fault and I apologize for it.

MEMORANDUM

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

TO : Frances O. Kelsey, Ph.D., M.D.
Director, Scientific Investigations Staff, HFD-108

DATE: FEB 10 1977

FROM : M. Adrian Gross
Scientific Investigations Staff, HFD-108

SUBJECT: Industrial BioTest (IBT) Response of 11/11/76 to Dr. Leventhal's Letter of 09/29/76 (Part I of 2 parts)

The following are my comments on IBT's written response; the IBT communication consists of 110 pages on the Naprosyn issue and 12 pages on the Isoprinosine one. I shall deal here only with the first of these since there is some priority attached to it due to other reasons. My comments on the Isoprinosine situation will follow separately in Part 2 of this memorandum.

I. General Impressions, Conclusions and Recommendations

Although in his letter, Dr. Leventhal invited IBT to present all their results of a comprehensive audit of the Naprosyn study, IBT choose not to do this. Instead, in their discussions of specific problems, they limit themselves generally to the few illustrations we have cited for them as examples of such specific difficulties.

We do not know at this point whether IBT prefer not to reveal to us information which they may perceive as being potentially damaging to them, or that they are incapable of conducting a thorough and searching "quality control" type of audit of a study executed by them. If the latter is true, I should think the reliability of this organization to undertake responsible and meaningful studies of this sort, both now and in the future, is very much in doubt.

For some of those issues in Dr. Leventhal's letter IBT choose to discuss, their general tone appears to be shrill and strident. There is much "legal-type" argument in reference to our concern over the non-availability of a substantial part of the records associated with this work. They dispute, (ineffectively, I might add) and dismiss our concern that reported data should be in accord with original observations. They even go as far as to suggest that they ought to decide what is reportable and what is not.

IBT give us the results of their own "analysis" of certain problems without elaborating on just how such an analysis was made. Their "explanations" tend to be no explanation at all, but merely conjecture and speculation which, at best, are seriously faulty. This pertains to the very extensive issue concerning the identity of the animals on test which is not limited merely to the body weight records.

Much of what we see in the IBT response is irrelevant, e.g. whether certain lesions can or cannot be recognized in an autolyzed carcass. Other arguments they make center on trivialities, such as the distinction between assessing the condition of the animals on test and examining the animals.

Some of the IBT statements boggle the mind as far as their credibility is concerned; they are asking us to believe, for instance, that all ante-mortem observations for each animal of this 22 months study were kept on "cage cards" or that the IBT technicians "kept in mind" the changes observed in these animals.

Much of the "logic" used by IBT in their arguments does not make any sense whatsoever. Examples: the technicians were well-trained and competent because they used certain terms common in pathology; the means for certain body weights could not be false since they were "consistent" with other means; changes observed in these animals do not mean much since they are commonly observed in aging rats, etc.

Still other statements by IBT represent certain situations in ways that we have good reason to believe were not the true ones; one such example is the allegedly bi-weekly interval of weighing the animals. There are other likely distortions of the truth presented by IBT here such as the meaning of "bleeding death" and that certain discrepancies were the result of mere rounding-off errors, transcription errors and other such "clerical" mistakes. IBT is also not above insinuating they had no knowledge that their report would be submitted to the FDA when the clear evidence in our hands is to the contrary.

More important and disappointing however, is the total inability by IBT to present any kind of acceptable explanation, analysis, evaluation, new information, etc. which would detract anything from the seriousness of any of the disturbing items mentioned in Dr. Leventhal's letter. Their generally self-righteous, indignant and unreconstructed attitude further suggests to me that they have no apologies whatsoever to make for the quality of this particular study. Nowhere do they indicate that the Naprosyn work was in any way an exception, a set of particular or unique circumstances converging into an unfortunate coincidence; on the contrary, IBT keep stating and implying ad nauseam that this was a properly executed and acceptable piece of work from which valid conclusions can be drawn or that the problems that we signal to them are "minor" and not "material."

Aside from this kind of posture IBT assume here, there is evident in their response something even more disquieting: the flawed perception IBT have as to the basic purpose of a toxicity trial and the widely accepted manner of conducting such studies. It seems to me that they do not understand the fundamental philosophy inherent in a safety experiment, both as it concerns execution and evaluation of the results.

Because of all of this I see no reason whatsoever that we should not continue to regard the Naprosyn work as totally unacceptable; I also see no reason for our not entertaining the view that all similar studies carried out by IBT in the past are likely in the same category unless shown otherwise by detailed audits of the data in their internal records.

Beyond these "regulatory" concerns there is yet another dimension which, at least in my own mind, is very likely - the matter of criminal violation of the law. This has in my view two distinct facets:

a) the clear evidence that material information on this study was withheld from IBT's report and false information substituted with the express purpose of deceiving both their client (Syntex) and the FDA.

b) a larger issue on which we may not have as clear evidence but on which such evidence could be developed with additional investigation - that this process of deception (in the sense of representing this entire study in such a manner that a favorable review would be made when, if the entire truth were known, no such favorable review could issue) was deliberate or purposeful.

Accordingly, my recommendations are as follows:

1. That we continue to view all such work (particularly long-term animal safety studies) generated by IBT as "suspect" until such time as additional detailed inspections resolve in an unambiguous manner whether such past studies are either "acceptable" or "non-acceptable." I would add here that it is essential such inspections be thorough and that they be carried out by experienced and competent FDA investigators. We can learn from the Naprosyn case itself that a searching and unbiased "audit" by the "client" of IBT in each case is unlikely, or, if likely, it is not probable that the results emerging from it will be shared with us.

2. That this entire matter be referred to compliance personnel case workers to evaluate the need for preparing a prosecution recommendation and the need for additional investigations as far as assessing individual responsibility is concerned. I have made similar recommendations on this matter as long ago as August 30, 1976 and as recently as January 14, 1977.

3. That a way should be found for alerting future potential clients of IBT of the difficulties they are likely to encounter with IBT work of this sort. Somehow unsuspecting such clients (including various agencies of the Federal Government which are current clients of IBT) ought to be protected against finding themselves in such unanticipated predicaments as currently experienced by Syntex and other past IBT clients.

II. More Detailed Comments

1. The problem of lack of records

While not denying such lack, IBT raises the following issues here:

a) is it reasonable to expect IBT to retrieve a complete set of such records on studies conducted in the past?

b) IBT has operated since 1952; its reports have been used by the government; it has an excellent reputation; it is a leading laboratory; it has worked for the government; its scientists are "conspicuous in laboratory circles"; it has been inspected by the FDA only once previously; no representative from the FDA or from any government agency has ever asked for such records; there is a problem with "FDA's historical disuse of such records"; there is confusion in industry on record retention; it is expensive to maintain such records; the FDA's own record retention may be "haphazard"; record retention is not part of any protocol requested by IBT's clients (including federal agencies); there is no requirement for this in FDA's "scientific literature" or in the FD&C Act; IBT does not feel it comes under the provisions of Section 704; records could be lost through "disaster, theft or even sabotage" and that charges to clients for such insurance would have to be made.

c) an independent research laboratory such as IBT often does not know how its work product will be used by its client. This tends to imply that IBT is unaware of the main purpose of safety testing - to support claims made in IND files, NDA's, ANDA's, food additive petitions, pesticide registrations, etc. My own reaction here is that at least in the case of Naprosyn (the study under specific reference in Dr. Leventhal's letter) IBT's client, Syntex, explicitly informed IBT that the study would be used by regulatory agencies in the U.S. as well as in other countries.

It seems to me that none of the excuses or the arguments presented by IBT here justifies a lack of records from any preclinical study, a report on which is submitted to a regulatory agency. I recall at this point that one of the initial problems discovered by us at Searle in 1974 was the claim by the firm that the records of one of their studies could not be located. Dr. D'Aguanno and others in the Bureau of Drugs were of the opinion at that time that without such records of original observations, the reports submitted to the FDA coult not be well differentiate from fiction.

2. On the problem that the lack of records casts doubt on whether certain procedures were carried out satisfactorily

IBT's response here is that "if one assumes bad faith, it would be more sensible to fabricate a needed record than to purposely 'lose' a record which would be conspicuous by its absence." It is unclear to me just what IBT has in mind with this reference to "bad faith." It is entirely possible that certain work which was supposed to have been carried out at a certain time was in fact carried out at a time other than the one

reported or not carried out at all. One likely reason for records of a certain kind not existing is that no observations to be recorded were in fact made. If then the report emanating from IBT implies that such observations were made at the proper time if in fact they were not or that they were made at any time when in fact they were not, would this not constitute "bad faith"? Why is it necessary to "fabricate" or falsify a certain record to indicate "bad faith" particularly when the company had no expectation of any imminent inspection or of any specific request for such records (see IBT's response - paragraph 1, page 7)?

In Dr. Leventhal's letter the issue of "bad faith" (in the sense of criminal responsibility, fraud, etc.) is not even alluded to, much less mentioned. His principal and only concern was the reliability of the scientific data generated by IBT - if there are no background records to substantiate statements made in a certain report submitted to the FDA, how is one to ascertain the validity of such statements? Furthermore, why does IBT imagine that their own client, Syntex, in not accepting the initial full report by IBT of this study, insisted to IBT that it supply authentic and accurate specific data for the conclusions reached by IBT? Is anyone to base an evaluation of the safety of agents tested by IBT merely on the general impressions gathered by IBT technicians or other workers?

Now that the issue of "bad faith" has been raised by IBT, all we can state is that we cannot exclude the possibility of this in the sense of observations having been reported by the firm when such observations were in fact not made. On the other hand, we do have evidence that certain actual observations were in fact made (such as tumors recorded by professional pathologists following microscopic examination of tissue) but such observations were withheld from the report originally submitted to the FDA. Could this sort of thing be viewed as "bad faith"?

3) <u>The problem of lack of records for ante-mortem observations</u>

IBT's response here is that the study protocol did not specify "daily physical examination" but they concede that it specified "general condition and behavior - daily." Inasmuch as the condition of the animals can be ascertained only on their being examined, this distinction appears trivial to me.

IBT further assert here that such "systematic records did exist for purposes of the study," but they admit such records are not now available. Are IBT to be believed here? Let us assume, for a moment, that ante-mortem records were in fact kept on cage cards (as IBT claim). Is this a satisfactory method of record keeping? A cage card (and we have seen those in use at IBT in other studies) is, at most, of a few square inches in area, a large part of which is taken up by the animal's identifying number. Is it then possible to have kept on such a space in a legible manner records of up to some 670 daily observations (22 months)? Is this a credible situation?

In the second paragraph of page 16 IBT state that "the observations on the cage cards were used for the direct transfer of information from time to time to the necropsy log (sometimes called the Histo-Path Logistics sheet), or path observation forms or animal disposition sheets, and in this case they were transferred as well to the pathology sheets incorporated in the study report and identified as Appendix II." Inasmuch as we have examined each of the 30 pathology sheets shown to us by IBT and the entire (7 pages) necropsy log as well as the entire (42 pages) Appendix II (we have never been shown anything termed "animal disposition sheets" and we presume this does not exist anymore, if it ever did) and we could not find a single note on anything that can be termed an ante-mortem observation, there are only two mutually exclussive conclusions to be drawn here:

a) either no ante-mortem observations of any kind were ever made in any of the 160 animals in this study, most of which died with illness during the 22 months of the experiment, or

b) IBT is asking us to believe what appears to be a vast falsehood on the "transfer" of ante-mortem observations.

The "study book" mentioned in the third paragraph of page 16 of IBT's response is another kind of record which has never been shown to us despite requests that we be provided with all records from the Naprosyn study. We can presume that, as with the "animal disposition sheets" mentioned in the previous paragraph, this is yet another form of the vanishing records from this study.

We have noted - as mentioned in the third paragraph of page 16 of IBT's response - that certain entries referring to some ante-mortem observations are present on the body weight records - see paragraph 2 on page 4 of the Hein-Gross memorandum of 8/10/76; however, as noted there, observations on certain lesions such as tumors were entered on the body weight records only sporadically and they were insufficiently well characterized to be of any meaningful value.

In conclusion then, I would tend to stick with our characterization that IBT did not have a systematic record of ante-mortem observations which includes details of externally visible tissue masses likely to be tumors. We expect in such records particulars on the anatomic site of such masses, details on their size, shape, appearance and, most important, progress with respect to time which is indicative of rates of growth and likely malignancy status. None of these is present in whatever notes appear on the periodic body weight records that we have been shown by IBT. We emphasize again that the study protocol submitted to the IND file and the NDA called for daily assessment of the animal' condition. Such entries of ante-mortem observations as are present on the body weight charts are, furthermore, unsatisfactory and confusing as explained on pages 4 and 5 of the Hein-Gross memorandum appended to the inspection report.

Paragraph 4 on page 16 of the IBT response asserts that the "available records... represent(s) a reliable matrix of information adequate to confirm any significant observations properly reportable in the context of a toxicity study." I would reject this notion that a contracting (or any) laboratory carrying out a preclinical study to be submitted to an NDA or an IND file has the option to determine which observations are "significant" to be "properly reportable." If this were so, carried to its logical extreme, it would suffice for such a laboratory to submit a report in which there could appear but a single sentence to the effect that some chemical agent has been tested and, in the opinion of that laboratory, no "significant" observations were made to be "properly reportable." Would this suffice for our purposes?

The bottom of page 16 and continued on page 17 of the IBT response describes the weighing procedure for the animals in use at IBT and what is "the technician's custom": - to make it "likely that he would see corneal opacities, if they are present"; this particular gem is sufficiently eloquent on its own so that no further remarks on our part are necessary.

Much the same can be said for the next paragraph on page 17 of IBT's response: "During the weighing period, the general condition of the animals is kept in mind by the technician; and if a pattern of findings is noted, it would be discussed with the project leader." How a technician can "keep in mind" the condition of each of the 160 animals on test from week to week and not confuse it with that of many other animals on other studies is hard for me to appreciate unless such technician were endowed with the memory of a genius. We are further being asked to depend on this technician to search this prodigious memory of his and only if he notes a "pattern of findings" would he "discuss" this with his project leader. This entire modus operandi is too ludicrous for words. Perhaps, however, what IBT means here is that the technicians keep in mind abnormalities only during a single weighing period. If so, suppose at some weighing date a single animal in some group is observed to have developed a tumor since the last weighing. Does this constitute a "pattern of findings"? Does it need "discussion with the project leader"? More important, does this need recording?

I might add here that in our examination of the IBT records on these studies we have not seen any notations of any such "discussions with project leaders" or of any remarks made by any such person. We are also unable to imagine precisely who functioned with this title of "project leader." The report on the Naprosyn study submitted to the FDA is signed by Philip S. Smith, Assistant Toxicologist, Rat Toxicity; by James B. Plank, Senior Group Leader, Rat Toxicity; by Paul L. Wright, Ph.D., Senior Head, Toxicology, and by M.L. Keplinger, Ph.D., manager, Toxicology. The Histo-Path Logistics Sheet for this project which is stated to have been initiated on 11/25/69 is signed by Michael R. Black, Technician in Charge, by the Departmental Director J. Plank (on 12/1/69) and by the

Pathology Departmental Director, L. Happ (on 12/10/69). The last mentioned individual is no more than a technician who usually carries out the dissection of the dead animals. Who then was the "project leader" here?

The two paragraphs at the end of page 17 of IBT's response deal some more with "IBT's practice at the time to record only positive observations"; this sort of thing provides no assurance whatsoever that observations were in fact made at all such times as IBT reports on these studies indicate they were made. The absence of all such observations (i.e. not only those associated with "positive" findings) leads to an inability by anyone to make an independent evaluation of the effects of the agent tested. Thus we remain unpersuaded that the lack of complete records from these studies is not critical to the acceptability of such studies.

4. The problem of lack of weighing records

At the beginning of this section on page 18, IBT starts off with a dispute based on some calculations which are predicated on misinformation - the duration of the study was 22 months and not 18 months. Since the protocol submitted to both the IND file and the NDA specifies weekly weighing of the animals and since 22 months is just 2 months short of 2 years (108 weeks plus 2 days) there should have taken place approximately 100 weighings, exactly what we had estimated.

Contrary to what is stated in the protocol (weekly weighing) and what is stated in the study report (monthly intervals after the first 13 weeks) IBT now say that weighings were carried out weekly for the first 13 weeks and approximately bi-weekly thereafter (end of paragraph 1 of their page 18). I believe that neither of these accounts are true as I shall demonstrate shortly. Suppose, for a moment, that the bi-weekly interval story is the factual one; take the first 13 weeks and add to this one half the difference between approximately 100 and 13 or approximately 87 which is 13+43.5 or approximately 56 weighings. But even this is far in excess of only the 33 weighings on which IBT has records.

Note at the bottom of page 18 of the IBT response that they admit having no records for 7 of the first 13 weeks and for a 5-months period. But means for all of these were reported by IBT; if the unavailability of records for all these and for other weighings can be explained simply on the grounds that no such weighings in fact took place, the reporting of such means would constitute nothing but causing fictitious (false) information to be submitted to the government with full prior knowledge by IBT.

At the bottom of their page 18 IBT state that "this is of little or no substantive consequence because:

a) such means as were reported were "consistent"; we do not question their consistency amongst themselves but rather their authenticity.

b) an "extrapolation" can confirm the value of the missing data. What if the possibly fabricated data were selected as a result of such an "extrapolation" process? Would this tend to make this entire business more palatable? Or, to put it in IBT's own words (first full paragraph of their page 19): "of virtually no consequence whatsoever" or "an absence of unimportant data"?

As to the contention by IBT that weighings were carried out weekly for the first 13 weeks and at approximately bi-weekly intervals thereafter, let us turn to pages 33-40 of the IBT response where they had prepared a list of weighings dates for which records are said by them to be available. The following are these dates and the intervening intervals between them in number of days:

Date	Interval in number of days
11/25/69	date study is alleged by IBT to have start
01/09/70	45
01/20/70	11
01/30/70	10
02/20/70	21
02/27/70	7
03/06/70	7
03/13/70	7
05/06/70	54
09/28/70	145
10/05/70	7
10/12/70	7
10/20/70	8
10/26/70	6
01/21/71	87
02/04/71	14
02/11/71	7
02/16/71	5
03/10/71	22
03/18/71	8
04/05/71	18
04/13/71	8
04/21/71	8
04/27/71	6
05/15/71	18
05/24/71	9
06/01/71	8
06/08/71	7
06/23/71	15
06/30/71	7
07/16/71	16
07/27/71	11
08/09/71	13
09/15/71	37

Note that:

(a) IBT say in their response (bottom of page 18) that "individual weight data have not been located for 7 of the first 13 weeks..." - this implies that they have been located for 6 of these first 13 weeks. In fact, however, as can be ascertained from the list above they have records for only 4 of the required 14 weighings (13 plus another one before the study started as IBT has in its report) in the first 13 x 7 = 91 days. In other words it appears that IBT are not being quite candid with us even as late as November 11, 1976, the date of their response.

(b) As to their contention that after 13 weeks weighings were carried ou "approximately bi-weekly" (paragraph 1, page 18) it is quite likely this is yet another falsehood: even if it were true that weighings were carried out at 14-day intervals and that the unavailability of most of these records is explainable on the grounds of their getting lost, it would follow that the intervals between successive weighings on which records exist would be divisible by 14. Note, however, in the list given above that only one such interval is divisible by 14 - 14 itself between 1/21/71 and 2/04/71 - and that none of the other 32 intervals are divisible by 14.

What I am inclined to believe from all this is the following:

a) weighings were carried out at most at variable intervals of time (5, 6, 7, 8, 9, 10, 11, 13, 14, 15, 16, etc. days) i.e. almost never at bi-weekly or monthly intervals.

b) that the unavailability of most of the body weight records required by the study protocol is not likely due to such records becoming lost, but rather to their never having existed in the first place.

c) that the information supplied to the FDA where IBT reports mean body weights for weeks 0 to 13 inclusive and at monthly intervals is, with great likelihood, false.

At the bottom of page 19 of the IBT response we are being presented with yet another canard: rodent studies such as this are not "designed as individual animal studies." Reading further into this remarkable paragraph continued on page 20, all I can say is that I have no knowledge of anyone in the FDA ever having claimed that "IBT has been a leader in the industry"; at most what we may have stated is that IBT is the largest (or among the largest) contract research companies in this field and in this country. But this need not imply that we necessarily believe the practices in use at IBT are the best in the industry. As a matter of fact I would state without any equivocation whatsoever that on the basis of what I have seen (and I have inspected a fair number of establishments on work of this sort in the last 12 years) that IBT is amongst the worst in the industry.

At any rate, it is simply not true that any experimental animal study required by the FDA at any time was designed in such a way that individual animal values are not of any importance. While mean group values are used in the review and evaluation process, if the individual values from which such means are computed are unreliable, so are the group means. This is essentially what we have been contending all along. If the mean values reported by IBT cannot be relied upon, of what value is their entire study? Yet both IBT and their client Syntex pretend now that the individual values are of no significance - in fact IBT goes further than that by asserting that they never were of any significance in any study required by the FDA, and they ought to know since, according to them, we say they are the leaders in the industry. Such is their logic for whatever it is worth. We have a different opinion on this issue which has been discussed at greater length in my memorandum to you of August 30, 1976 on the very same study with which we are concerned here.

The last paragraph on IBT's page 20 reveals yet another problem with their operations: they state there that a statistical analysis by Syntex of the data collected by IBT in the study under reference revealed a "statistically significant" decrease in body weights of male rats at the top dosage level. Yet if we read IBT's own original report to Syntex (the one submitted to the FDA) we find on page 9 there that although statistical analysis of body weights was carried out by IBT (see the reference to the body weight of females not being statistically significant) the decrease in body weight of the top level males, although mentioned, is, nevertheless, not signalled as being statistically significant Is this another example of mere incompetence in statistics at IBT (several have been cited to them previously by this writer) or an issue of deliberately not revealing significant drug effects elicited during the study? I am surprised not to read here what is the standard excuse of IBT with issues of this sort - a minor clerical error of no significance whatsoever.

5. The problem of the missing gross pathology observation records

This issue starts on page 21 of the IBT response with the usual rhetoric of argument characteristic of this communication; I shall omit any comments on most of this page which strikes me as meaningless.

Near its bottom, however, we find the admission "it is true that some items of records are not available..." The next paragraph, the first full one on page 22, contains some falsehoods and is, in general, grossly misleading. Before we tackle this, some clarification is necessary.

What exactly do we have reference to? The answer is simple and it is precisely stated in Dr. Leventhal's letter to IBT: records of gross pathology observations. What is usually meant by this term is not difficult to appreciate: the records of the observer of grossly visible lesions at the post-mortem examination of the animals. What we wish to specifically exclude from this term is any lists of lesions which have been compiled by someone other than the observer, whether these are the so-called "necropsy log" (which, we have been told was compiled by a clerk who did not do the post-mortem examination), whether these are the so-called "animal disposition forms" (which we have not had the priviledge to be shown by IBT and which we believe do not exist today, if they ever did), whether they are in Appendix II of the IBT report to Syntex (which we were told by Mr. Plank, who made no observations at the post-mortem examinations, he compiled himself) or whether such lists were provided by Syntex in their attempt at "reconciliation" of the pathology data. Syntex knows no more about these observations than we do or, for that matter, than the man in the moon.

It appears that IBT are either incapable or unwilling to understand (or pretend not to understand) that we are challenging the validity of the information provided in their report which had been submitted to the FDA. Just because there is a multitude of entries of pathology terms scattered all over the map does not by itself make such information valid, or authentic, or reliable.

Since we were not present at the post-mortem examination of the animals, the only means we have to validate the data submitted to the FDA is to check it against the original observations. If the vast majority of such observations do not exist, neither the FDA, nor Syntex, nor IBT themselves can validate the information reported.

The only original records of post-mortem examinations, as stated above, are those made by the observers themselves. All other such "data" are no more than transcriptions of doubtful reliability (as amply demonstrated in the Hein-Gross memorandum referred to earlier here). To distinguish them clearly from original observations, we may use for them the term "derived data." The figure of "approximately 80%" mentioned in Dr. Leventhal's letter and with which IBT takes issue, is, therefore, not unimportant nor does it refer to mere "pieces of paper" as contemptibly dismissed in paragraph 3 of page 21 of the IBT response. The Hein-Gross memorandum of 8/10/76 states at the middle of page 3 that for the 160 animals in this study original records of gross pathology examination exist for only 30 of these animals. This fact, which cannot be disputed by IBT, is equivalent to saying that 130 such records are missing and 130/160 = 81.25%. Simple, is it not?

Yet IBT persists in obfuscating this issue - first full paragraph of their page 22: "Data on gross pathology findings for post-mortem animals were compiled from cage cards and animal disposition forms and from the necropsy log." The necropsy log is not an original source of records; neither can the mysterious "animal disposition forms" be an original such source. Read, for instance what IBT state at the bottom of page 23: "The fidelity with which the information on the available pathological observations sheets was transferred to the available necropsy log goes a long way to reassure anyone of the fidelity of other data transcribed from other sources which happen to be unavailable." All right, then, let us say we are persuaded by IBT on the "fidelity" with which any pathologic observations from any original source (whether records of such original observations exist today or not). What does this say? It says, at least to me, that the necropsy log contains a full account of all gross pathology observations; in other words, there culd not be anywhere, at any time, any original such observations which did not find their way into the necropsy log. That much is clear.

Yet what do we find in this necropsy log? Among other things, we find there that for over one-third of all animals started in this study (and, simultaneously, for one-half of all animals that died before the end of the observation period - 22 months) the notation TBD/TDA or TBT/NTT is made in the necropsy log. We were told at IBT this says: "Too badly decomposed/technician destroyed animal or (for NTT) no tissues taken (presumably for histopathologic examination). Interestingly, for only one of the 55 animals with a TBD entry was there any kind of grossly observable lesions noted.

If we compare what this necropsy log indicates for these (54 cr) 55 TBD animals with what has been reported by IBT to Syntex (and by Syntex to the FDA), we find that in all cases but ~~five~~ of these, grossly visible lesions have in fact been entered for these animals.

This entire issue is discussed at greater length in my memorandum to Dr. Finkel of 1/14/77 on Naprosyn - pages 12-16 there. That section concludes with an analysis of the likely motives for this vast, apparently deliberate, process of deception, and with a recommendation for prosecution of IBT and/or others.

The second full paragraph on page 22 of the IBT response refers to a Syntex "analysis" of the data; I shall not comment at any length on this since our concern is not with any "analysis" but rather with the data themselves and, on this, Syntex, as we have said above, has no direct knowledge.

The last paragraph on page 22 of the IBT response states that "records exist to substantiate gross pathologic examinations of 144 of the 160 animals..." which is highly misleading; if we limit our attention to merely records of original observations, the figure is merely 30 of the 160 animals, as we have already noted.

In the first paragraph on page 23 we read "The detailed findings reported are such as to give assurance that careful examinations were conducted. For example, untrained and inexperienced personnel are unlikely to make the observations they did like cystic ovaries, undescended testes, hydrometra, and the like." We have already discussed both here and in my memorandum to Dr. Finkel of 1/14/77 just how "detailed" the findings on gross observations were, particularly for the 55 TBD animals. Whether this sort of thing gives "assurance that careful examinations were conducted" is self-evident. As to the training and experience of the personnel involved in making these observations, particularly the basis given by IBT for anyone's ascertaining of the competence of these people (their use of words of more than one syllable) this is also in need of no further comment.

It is interesting to note that, when it suits their purpose, IBT are less than assuring about the technical terminology used by the observers of pathological material. For instance, in the middle of page 61 we read the following concerning "IBT vernacular and internal procedure":

"A number of the gross observations which may not have found their way into the report were the result of the oversophistication of knowledgeable technicians. The animal room and necropsy technicians are known to have had such pride that they would be inclined to 'show off' their knowledge by using histological terms like 'adenoma' to describe a suspect gross observation. Similarly, the word 'tumor' was being used loosely by IBT personnel internally to describe enlargements which often proved not to be neoplasms at all. This was true during the period of this study."

Also in this connection note first full paragraph on page 29: "... technician-surmised 'tumors' are often mere enlargements which may disappear naturally."

What is perhaps more significant here is that we expected from IBT a full account of the sort of problems we cited to them with this study - see Dr. Leventhal's next to the last paragraph in his letter to IBT of 09/29/76. Not only do we not get this from IBT but we are instead being offered mainly arguments, disputes, and meaningless generalities such as "in a few instances."

The middle paragraph on page 23 of the IBT response indicates that "The available and reported findings were essentially those to be expected in a population of aging rats." We did not expect in rats almost two years old changes characteristic of newborn rats. This paragraph of IBT's

implies that, except for stomach lesions, all other changes observed are merely incidental or not drug-related. We are grateful for this opinion of theirs but such a conclusion on their part cannot be verified unless all changes observed (gross and microscopic) are properly reported and subjected to analysis. It would not be completely unheard of if other drug-related changes (tumors, for example) were to be present in this study and yet such changes would be identical to those seen in unexposed older rats.

I have already commented on the paragraph starting at the bottom of page 23.

The final paragraph of this section (page 24) is a "summary" of IBT's assessment that "the sole problem is the absence of just records and the problem is not one of the absence of data." In view of what we have presented here, particularly with reference to the TBD animals, IBT has, in my view, a rather serious problem with the data they report when such data are viewed against the records that are available.

6. The problem with missing records from clinical pathology laboratory determinations

This is admitted by IBT with the hope that such records "may someday show up..."

They also express having "every reason to believe the determinations reported are accurate."

7. The problem with the eye examinations

There is over a page of comments on this by IBT but nothing really responsive: the protocol for the study (agreed to by Syntex and IBT, and submitted to the IND and NDA) called for ophthalmoscopic and slit-lamp examinations; the clear implication to a reviewer is that such examinations were carried out. IBT now admits these were in fact not carried out. This omission was not adressed in IBT's original report.

8. The problem of the confusion regarding the identity of the animals on test

The IBT response here, starting on page 28 begins with the assertion "There is no confusion as to animal identity data presented in the IBT report." I can fully agree with this, but then Dr. Leventhal's letter was not concerned with the report. His statement was, "There seems to be confusion on the identity of the animals on test." How do we get such ideas? From the IBT report? Hardly. Rather it seems so to us after examining the internal records on this study kept by IBT. We find these as not being well reflected in the IBT report.

Following another reference to the Syntex analysis, IBT get down in paragraph 2 of page 28 to admitting the existence of errors which they characterize as "clerical errors." These are, according to them, "not identity errors but recording errors." Just what are IBT's views as to the difference between these two kinds of errors is unclear to me and IBT shed no light on how they arrived at this determination.

I can see that someone may (by some kind of "recording error") write down the number of, say, animal 43, as, say, 48 by mistake at a certain given time, i.e. once. What I cannot see is how an animal that is indicated as being dead (through its sudden disappearance from weight records or through other notations in other records) is indicated as being alive for up to 8 or 10 or more subsequent weighings (see Hein-Gross memorandum of 8/10/76 - bottom of page 5 for a few examples of this) without this constituting a change in that animal's identity. Even if we accept Syntex' analysis on this problem, and it is clear from my memorandum to Dr. Kelsey of 8/30/76 on this that there are serious problems with their hypothesis, the conclusion must follow that identity problems with these animals were persistent for long periods of experimental time. Moreover, the numerous instances indicated in the Hein-Gross memorandum of 08/10/76 where animals are indicated to have died repeatedly (sometimes with different sets of lesions) provide additional evidence that problems with the identity of the animals are not limited merely to body weight records; as such, they cannot be as easily explained away as both Syntex and IBT attempt to do with their "adjacent cage" theory, a conjectural type of analysis of doubtful plausibility at best.

The next point made by IBT here (paragraph before last on page 28) states "...the IBT study was premised upon the objective of determining the drug-related effects in relation to test <u>groups</u>- <u>not</u> individual animals."

What this implies is that IBT believes it is not the individual animal values that matter but, rather, the group averages or means. My answer here is that such group averages as are reported by IBT are necessarily based on individual values and the reliability of the former is a function of the reliability of the latter. Furthermore, in order to answer whether a certain group average (mean) is different in a "significant" manner from that of some other group (the essence of comparison) the variance of the <u>correct</u> individual values must be known.

The last paragraph on page 28 states: "...The only significance lies in the events, and conclusion drawn from intergroup comparison." As explained just above, without knowing the correct individual values, no intergroup comparisons can be made in any valid scientific sense. Moreover, no conclusions whatsoever can be drawn from any comparisons if one has serious questions on the validity of the essential data base.

The first full paragraph on page 29 gives a hypothetical example: "suppose as a matter of reconstructed fact a tumor is recorded as a gross observation for animal Y instead of animal X in the same group, and the tumor is histologically confirmed and reported as to X". IBT then asks a rhetorical question: "What difference can the error make scientifically"? IBT provides its own answer: "None."

The example given by IBT, even though hypothetical, is impossible for me to visualize as capable of happening: suppose animal X has a tumor, but through some error at autopsy the animal's identity is mistakenly identified as Y, how on earth is it possible for the histopathologist to report such a tumor for animal X unless he was endowed with remarkable clairvoyance? I would be interested in seeing even a single actual case where IBT can document that the hypothetical example they gave here has occurred in reality. And if they cannot do this, their hypothetical example has no value. What is the "difference" errors in misidentifying animals with tumor can "make scientifically"? Unlike the answer given by IBT here ("None") I would say that such "difference" can be enormous as far as assessing the safety of the agent on test. Suppose, for instance, that one or more tumorous animals recorded in error as being such had died near the end of their lifespan; also assume that the correct animals that had such tumors (and which, as a consequence of the same error, are not recorded as tumor-bearers) in fact succumbed with such tumors at a relatively early age, long before any control animals exhibit any tumors whatsoever. Could we not be dealing here with a highly potent carcinogen, yet through the ineptness of those involved with this study, this kind of evaluation cannot possibly be made by anyone?

What IBT are saying implicitly through their example, through their question and answer as well as through what preceded these in this section (the inference that individual animal data are of only peripheral if any importance, and that it is rather the total "body count" that really matters) betrays to me a basic lack of appreciation at IBT of the fundamental scientific purposes, design and execution of a toxicology study. It seems to me that not only did they mess up this particular study through sheer carelessness, lack of supervision by responsible and competent professional scientists, a casual attitude about recording observations, lack of maintenance of records which could aid clarifying what really happened in the study, etc., but they are either incapable or unwilling to carry out any kind of study like this in a proper and accepted fashion.

The large paragraph on page 29 of the IBT response deals with what I believe is likely a myth as well as a fallacy: that "group testing" and "group reporting" are "generally recognized as ...scientific realities" and that the evidence for this is "the prevalence of group caging at that time" (presumably the time this experiment was carried out). This, to my view, is unadulterated nonsense. I know of no long-term toxicity study of the kind we are discussing here, whether the animals were housed individually or in groups or more than one to a cage, where we have accepted the data of such study without an impression that correct individual animal data were available. I cannot see any inconsistency in a situation where animals are group-caged or group-housed and their being simulatneously individually identified. In fact, I know of several actual specific studies carried out on this basis.

The bottom third of page 29 and the top of page 30 in the IBT response refer to a number of procedures said to be in effect at IBT at the time of this study; their purpose, we are being told, was "precautionary" presumably to avoid intergroup mixups of animals. My own comment on this is that if such measures as removing only one animals from its cage at any given time from weighing did not prevent intra-group misidentification (conceded as having been present by both IBT and Syntex) how can we be assured that despite all the measures listed there by IBT intergroup mixups of animals could not have taken place?

The middle paragraph on page 30 states: "...there are of course more clerical errors than were used as examples in Dr. Leventhal's letter." In a sense, this is some kind of admission on the scope of the problem here; on the other hand, I do not believe Dr. Leventhal's letter had any specific reference to "clerical errors" as this statement may imply.

I do not agree with what we read further in this paragraph: "The crux of the matter lies, however, in the ability to rationally reconcile or explain the obvious cause of the error and weigh the implications of the corrected data in relation to the report." What I believe is the "crux of the matter" here is the sheer weight or abundance of errors and what this says about the reliability of this study. Moreover, in the sense that the importance of these errors is apparently discounted or not recognized (even disputed) by IBT, I believe there is good reason to question the reliability of any other toxicology study carried out by IBT. And it is this kind of concern which had prompted Dr. Leventhal's letter to IBT in the first place - we have already reached our conclusions on the acceptability of the Naprosyn study under reference here; what worries us is all <u>other</u> similar studies carried out by IBT. I, for one, do not find the IBT response as being in any way reassuring in this respect.

The rest of this section from the bottom of page 30 through page 40 deals with the analysis "to resolve the identity of the animals on test." This entire effort looks remarkably similar to what Syntex had presented before us and in writing last August (on which I commented in my memorandum to you of 8/30/76) and again last December (on which I addressed a requested review to Dr. Finkel on 1/14/77). I can summarize this entire "analysis" or "reconstruction" with the following observations:

a) Contrary to what IBT state in their bottom paragraph of page 30 as to what such an analysis can "readily determine," my view is that the speculations as to what weight belonged to what animal on any given day are no more than that - speculations.

b) The "adjacent cage" theory cannot account for the many animals apparently dying repeatedly or for such repeated deaths being associated with different sets of lesions; nor can it account for conflicting accounts between different pathology records or between what we see in internal IBT such records and what is reported to the FDA.

c) The "adjacent cage" theory developed by Syntex and/or IBT cannot account for all problems on identity of the animals on test as far as body weight records are concerned; witness their set of "irreconcilable differences."

d) As stated previously here, I cannot see how any such review by Syntex or IBT or both can achieve what is stated in the first line of page 31 of the IBT response: "Our review established the fact that clerical errors of body weights within groups (as opposed to between groups) accounted for the appearance of the discrepancies in body weight, dates of death, multiple deaths, and animal resurrections" (my own emphasis). If all of these are ascribable to "clerical errors" and if clerical errors can be dismissed so lightly, what, pray, is a serious impropriety in any study that can be "established"(?) to be due to some reason other than a "clerical error"?

9. The problem with animals being weighed alive subsequent to dates of death

The section in Dr. Leventhal's letter to IBT pertaining to this issue lists 9 examples of animals in this category. It is significant to note that IBT's response on this issue (pages 41-42) addresses only these 9 animals, all chosen by us from merely the control group, and none others. I am wondering whether they found any other animals with this problem in this entire study and they elect not to report on these, or they are incapable of discovering other similar cases. At any rate, the IBT response here is completely inadequate even with respect to the cases they choose to address. Items:

a) IBT response, paragraph 2, page 41: "According to the IBT report, animal 12 was a sacrificed animal; hence there could not have been any weighings reported after death." It is true that the IBT reports this as a terminally sacrificed animal but our source was not the IBT report; it was rather the original body weight records we found at IBT. The record dated 5/15/71 shows in the weight column for this animal a dash and we were told at IBT that such dashes in the body weight records indicate that the respective animals were dead on the day the records were made. Indeed "neighboring" animals such as Nos. 9, 10, 11, etc. (admitted by IBT to have died previously to that date) are indicated by similar dashes. Now, if animal 12 was not dead on 5/15/71 where was it at the time of weighing? Was it in downtown Chicago, taking in a movie perhaps? And, is it not true that for dates subsequent to 5/15/71 animal No. 12, whether dead or alive, decided to rejoin its mates, as it were?

b) IBT response (same paragraph) as above: "Neither were there any recorded weighings after the reported death of animal 16." What we said above for animal 12 is essentially true also for animal 16 except that in this case its "dropping out" of the weight records was somewhat more prolonged: from early February to June 1971. There are 13 weighing records available during this interval and animal No. 16 is mysteriously absent in all of these only to reappear just as mysteriously later in June 1971.

c) IBT's response, last paragraph, page 41: "Somehow the FDA makes the same mistake regarding animals 21 and 32 as they did with regard to animals 12 and 16." IBT then refers to our "lack of perception," about our misleading ourselves and it reiterates: "...there were no weighings recorded after the reported deaths of animals 12, 16, 21 or 32."

For animal 21 the same applies as what we indicated for animals 12 and 16; this animal "dropped out" of the IBT weight records after 5/24/71 for at least five separate weighings only to reappear without explanation on 7/27/71. Animal 32 disappeared from weight records on 4/21/71 only to make its reappearance on 4/27/71.

d) For animals 13, 15, 20, 29, and 31 we are being referred to some tables where there are no explanations given by IBT yet they state (paragraph 3, page 41): "It would be a waste of words to describe them" (meaning the explanations) and (last paragraph, page 42) "...there seems to be no point in using words to describe the .... explanations as to animals 29 and 31."

The tables to which we are being referred are remarkably similar to those presented to us by Syntex last summer. I have commented on those tables at length in my memorandum to you of 8/30/76 where I gave many reasons for my belief that Syntex' "adjacent cage" theory will simply not wash. It is unclear to me at this point whether IBT endorses the Syntex speculations (through their reference to "no point in using words" or "it would be a waste of words") or they do not wish to associate themselves with that theory through apparently abstaining to make specific reference to it.

At any rate, the "adjacent cage" hypothesis cannot account (as can be plainly seen from the tables IBT include in their response) for the following:

1. the weight 840 gms recorded on 2/4/71 for animal No. 4; the "adjacent" animals (Nos. 3 and 5) were still alive at that time. This is conceded by IBT in paragraph 3 of page 41 of their response.

2. A similar situation exists with the weight of 825 gms on 5/15/71 for animal No. 13 - this weight seems to come from "nowhere."

3. Other weights unexplainable even by the questionable "adjacent cage" theory are: all the weights from 1/21/71 through 8/9/71 for animal 55 (there are at least 19 of these judging merely from available weight records) and this animal is indicated as being dead on 10/20/70; the weight of 550 gms recorded on 5/15/71 for animal No. 71; the weight of 745 gms. recorded on 5/24/71 foranimal No. 84; the weight of 840 gms. recorded on 2/4/71 for animal No. 88; the weight of 290 gms. recorded on 5/24/71 for animal No. 113, etc. etc.

In summary, IBT's "explanations" on this issue are not in any way convincing that the identity of these animals was not, to say the least, in vast disarray. Even if we are willing to accept Syntex' "reconstruction" here (and it is abundantly clear that this has no more than questionable merit, at best) this cannot justify what apparently went on at IBT during this study: lack of competence and reliability on the part of those entrusted with the execution of this study and on the part of their supervisors as well as a general cavalier attitude towards collecting research information. Even more distressing is the fact that at this late date, long after our pointing out to IBT their shortcomings, they seem to be unwilling to be candid about the facts as they and we know them - that weights of live animals were in fact recorded after IBT's own records clearly indicate such animals to be dead, e.g. animal No. 55 discussed above.

10. The problem of extreme weight changes on successive weighings

Here we again have a concession on the part of IBT but then this problem is dismissed by them on the grounds that "the conclusion(s) presented in the report on weight gains remain the same..." (page 43 of the IBT response).

11. The problem of two separate dates and two separate post-mortem examinations for animal 87.

IBT on page 44 of the response provides no explanation for this but, again, states this to be not "...material in the conclusions presented in the report" since (get this) "...the only finding was a lung abscess in one of the animals." Nothing need be added here.

12. The same problem for animal 102

We read here (paragraph 1 of page 45 of the IBT response) that: "IBT is not pleased with that fact, but for the most part it can be reconciled. Easily perceived clerical errors are involved which can't be of any real significance in terms of the report because nothing was reported except as to the real '102'."

Since I am sure that if I were to paraphrase the rest of this amazing story which sounds like a suspense thriller I would not be believed, it is reproduced here verbatim:

"By reference to the body weight data it can be confirmed that the animal recorded as being necropsied on June 23, 1971 is the real TII female animal 102. Animal 102 was first unavailable for weighing on June 23, 1971. Tissue from this animal was histologically examined and reported in Appendix II of the report."

"The animal recorded under '102' as being necropsied July 30, 1971 has to be the otherwise lost animal 101. Animal 101 was last weighed on July 27, 1971. The July 30, 1971 necropsy log entry makes note that the animal was a TII female, which of course fits animal 101. This '102' could only be animal 101."

"The third '102' was recorded as a TII male also necropsied on July 30, 1971. In this case a female number was used (i.e. '102'), but IBT doesn't perceive this as a sex mix-up but rather one of the necropsy technicians using the wrong number on the right animal. TII male animal was first available for weighing on July 27, 1971 so this is the most likely candidate for the third '102'."

Just how it can be "confirmed" by reference to body weight data that the animal "recorded as being necropsied on June 24, 1971" is the "real" TII female animal 102, is, of course, not explained by IBT. Neither is it explained how they can determine that the tissues histologically examined and reported in Appendix II come "from this" animal. The fact that the "animal was a TII female which of course fits animal 101" is rather unconvincing since this could "fit" 19 other animals. How did animal 101 get "lost" anyway? The weight records available indicate to me no such loss. I do not know exactly what IBT "doesn't perceive as a sex mix-up" - I certainly can imagine all kinds of sex mix-ups - and why is not the necropsy technician using the wrong number on the right animal "perceived" as a "sex mix-up"? There are a host of other questions that could be asked here but it is obvious that any credible answer from IBT is not likely to emerge here.

What do the IBT records actually indicate?

For the entry made on July 30, 1977 (the one for which IBT now say, "but IBT doesn't perceive this as a sex mix-up but rather one of the necropsy technician using the wrong number on the right animal" and then that "this (male animal 96) is the most likely candidate for the third '102'," there are 2 records we found at IBT:

a) the <u>original</u> record (the gross pathology sheet) says in plain words opposite the gonads for this animal "missexed"; it also has noted "pneu. +3" opposite the lungs and "hem." opposite the stomach. I emphasize, this is the <u>original</u> record, presumably made at the time of necropsy.

b) the necropsy log entry for 7/30/71 says for animal 102: missexed o marked o. Lungs pneu. +3. Stomach hem.

What IBT report grossly for animal 102 is just H (hemorrhage) for the lung - which is certainly not in accord with their records - and for animal 96 on which we cannot find any record in the necropsy log and there is no pathology sheet) IBT report P (pneumonia) for the lung.

All of this says to me the following:

a) the "explanation" on animal 102 in IBT's response does not seem to make any sense;

b) even if it were to make sense, the current IBT explanation for this animal is not a credible one;

c) even if it were so, it is still amply evident that there was mass confusion in IBT records;

d) by not revealing this confusion in the original report and by substituting there false data (false in the sense that they are not in accord with the data as in the internal records), IBT had deceived their client, Syntex, and through them the FDA on the reliability of this study.

e) by not having reference to other animals in this study where there were deaths listed on more than one date (see Hein-Gross memorandum of 8/10/76) IBT are not being entirely candid with us on the scope of this problem even at this time.

13. The problem with animal 40 (recorded as having undergone a "bleeding death" at a time when bleedings were not carried out)

The entire IBT response on this issue (page 47) is reproduced verbatim below:

"Animal 40 was on test for less than 3 months and could not have died as a result of bleeding for clinical chemistry studies. The animal was, however, necropsied and was found to have chronic tracheitis and murine pneumonia which could have caused the presence of fresh blood at death. From this the observer may have inartfully used the phrase 'bleeding death'."

"No one can be sure exactly what was in the mind of the observer at the time he wrote 'bleeding death', but it is extremely difficult to fabricate from this obscure situation something either ominous or significant."

Consider the following:

a) The original record of gross pathology examination (one of the few that were available) even though containing a space for date of death, does not indicate the date of death for this animal. In fact it indicates no observations whatsoever except for the weight of the animal; written clearly across the top of the sheet is the notation "bleeding death."

b) The necropsy log also does not indicate the date of death of this animal (even though space is provided for this specific information which is given for most other animals). Thus the exact date of death for this animal cannot be determined by anyone. Judging from the order of death (the necropsy log is arranged in more-or-less chronological order, though not rigidly so) one may estimate that this animal died sometime between 1/15/70 and 3/24/70, i.e. from somewhat short of three months to nearly five months into the study. The only gross changes noted in the necropsy log for this animal is "bleeding death", the same as in (a) above.

c) We were told by IBT personnel directly involved in these studies that the term "bleeding death" means at IBT the death of an animal while or very shortly after being subject to blood collection. During our audit on the study on Isoprinosine (referred to separately) we noted that there was an excessive number of animals for which the notation "bleeding death" appears, and, in response to our specific questions on this, that was the explanation for this term which was given to us. It made considerable sense since the dates of death of many such animals coincided with the dates of the periodic blood collections.

d) Despite what is present in both the original and transcribed records at IBT on the gross changes noted for this animal (i.e. nothing except "bleeding death") what do IBT report in the way of gross changes for this animal? Bleeding death? No, that could be somewhat embarrassing, particularly since no bleedings were carried out at that time. They choose, instead to report a purely fictitious change in the lungs of this animal - congestion.

e) Chronic tracheitis and murine pneumonia were said to have been found in this animal only on microscopic examination of the lungs. Neither of these two conditions can cause "the presence of fresh external blood at death" as mentioned in the IBT response. Their explanation, therefore, of the "observer may have inartfully used the phrase 'bleeding death'", not only does not make any sense but it is clearly not to be believed.

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This may be an "obscure situation" to IBT, but to me it bears considerable similarity to the issues that will be discussed in greater detail under subsection (16) here. I do believe that this kind of problem is highly "significant" (IBT's views notwithstanding here) and the reasons for this will be given once we reach subsection (16). Whether this is also "ominous" or not, remains to be seen at this time.

14. The problem of the variability of weights of animals within treatment groups at any given weighing

The IBT response here (page 48) consists in little more than a "categorical denial" of this charge. They cite here their "enormous amount of experience," that what is seen here ("except for ...isolated instances...") is to be expected and "of no material significance." We stand by the statements we have made in this regard. For examples on this issue, consult Hein-Gross memorandum of 8/10/76, pp. 6-8 there. Other instances can be readily gleaned from the tables pp. 33-40 provided by IBT in this response. The "material significance" of this issue is contributory to all others pertaining to the reliability of this study.

15. The problem of confusion on the sex of some of the animals in this study

The IBT response to this (page 49) starts with some venom (references to "transparent bias", "innuendo", "inaccuracy", "exaggeration", "combative", etc.) but then they get down to business and admit to the existence of at least two such cases.

Their "explanation" for these two cases (animals 20 and 102) are no explanations at all; the sort of thing they say now cannot be verified even by them (e.g. that animal 20 is in reality animal 21) and the "explanation" for animal 102 (given under subsection 12) was equally inadequate, as we have already seen here.

16. The problem with the autolysis of large numbers of these animals

There is nothing new in the IBT response here, beyond some gratuitous remarks addressed to us on "unjustified implications", "out of place" (statements), "external pressures" (influencing us), "incompetence" (of FDA reviewers), etc. which I shall ignore here.

This issue has been discussed in detail (see my memorandum to Dr. Finkel of 1/14/77) and, after reading the current IBT response, my conclusions are considerably strengthened. The basis for this can be found in the following:

a) the discussion under subsections 13, 18 and 27 here,

b) the IBT statement at the bottom of page 23: "The fidelity with which the information on the available pathological observation sheets was transferred to the available necropsy log goes a long way to reassure everyone of the fidelity of other data transcribed from other sources which happen to be unavailable. (The comparison of the pathology observation sheets with the necropsy log reveals a word-for-word accuracy of transcription.)"

c) nothing that I read on pages 51-58 for this subsection (16) induces me to question the validity of the analysis presented in the memorandum to Dr. Finkel of 1/14/77.

I would, therefore, re-emphasize the recommendation made there that thought be given to prosecution of IBT and/or others. A final such evaluation should be made only after professional compliance officers here also had a chance to analyze this situation in detail, review the exhibits collected during the inspection, recommend whether additional investigations relating to individual responsibilities are in order, etc.

I would also recall here that Mr. Hein and I called specific attention to this problem in our report of 8/10/76 (pages 17-19 there), and that my initial recommendation to have this issue referred to "compliance" for this sort of purpose was contained in a memorandum I wrote on 8/30/76. The type of analysis presented in my 1/14/77 memorandum can be viewed as representing in some way what I believe a professional compliance officer should have addressed on this issue; this should not be taken in any sense to indicate that I consider such input by Compliance personnel no longer necessary. My intentions are precisely the opposite: let them become involved and immersed in this situation (which I regard as extremely serious and of an unestimable large impact with reference to other studies conducted by IBT) as soon as possible.

17. <u>On the problem of the pathologic validity of lesions noted in decomposed tissues</u>

IBT state in their response here (page 59) that: "Pathologists are in general agreement that pulmonary congestion ... can be recognized in rats that are in advanced stages of autolysis." This may be so but it is not the point made here in Dr. Leventhal's letter. The issue is not one of "recognition" but rather of "validity" of this finding.

Speaking as a pathologist, my view (which, I venture to say, will be endorsed by any competent pathologist) is that pulmonary congestion seen in an animal that has been dead for some time is usually artefactual in the sense that it is most likely due to hypostatic forces rather than a result of any effects due to other causes. The same is true of pulmonary congestion in an animal (or human) which has been in a state

of recumbency for some time. Unless an observer is skilled in making the differentiation between hypostatic and other forms of pulmonary passive hyperemia (and some evidence of this is provided in the description of this lesion by the prosector in the report of grossly visible lesions) this kind of observation is of questionable value. From what I have seen on the kind of detail provided by the prosectors in this study as well as the quality of their professional supervision (if any), I would doubt very much that the prosectors in this study were aware of these distinctions.

The gist of what IBT state in their response in this subsection is completely irrelevant to our concern here. Their last sentence here is that they believe our "scientific point of view" is "erroneous". I would disagree with this characterization.

18. The problem with animals from which no tissues were collected for microscopic examination, yet reports on such examinations were nevertheless made

IBT state they know of only one such animal (i.e. they admit the seemingly impossible, unless we have another problem with confusion of identity of the animals on test or someone "fabricating" data) and this is animal No. 119. They state that for this animal, as well as for others, their "life histories can't be traced." We do not require tracing any animal's "life history" but we do expect that no animal be recorded as dying more than once, and that if it is stated that no tissues were sampled from that animal, no reports of examination of such tissues be provided. This is not an unreasonable attitude on our part.

In addition to animal 119 which IBT concede to be in this category of multiple deaths (but on which they did not comment under the pertinent subsections 11 and 12) we found at least another one with this problem:

Animal No. 22 is recorded in the necropsy log as being one of those TBD/NTT (too badly decomposed/no tissues taken); yet an IBT report on results of histopathologic examination of such tissues for this animal appears in the version submitted to the FDA. For this animal IBT cannot make even the lame excuse they made for No. 119 since only one entry for it appears in the necropsy log. Perhaps, this is the reason why IBT could not find this animal.

Note another interesting feature for some of these TBD/NTT animals which is similar to some of our comments for subsections 13 and 16:

Neither animal 22 nor 26 has any specific gross post-mortem observations recorded in the necropsy log. And yet for each of these two animals, neither of which is recorded more than once in that log, such specific gross post-mortem observations are reported by IBT. I would regard this as being of just as much significance as the case of animal 40 (subsection 13) and that of the TBD/TDA animals (subsection 16).

19-21. The problem of the tumors noted in the study being either improperly reported or not reported at all to the FDA

IBT begin the response here (page 61) by saying that they do not agree with our observation that pathology findings were either improperly reported to not reported at all. I have commented earlier in this memorandum on paragraph 2 here whose contents appear to me as being nothing short of preposterous.

Paragraph 3 contains another "sleeper": it refers to a "well-recognized idiosyncrasy": "...IBT's practice of not reporting all such gross observations of tumors unless they were confirmed at necropsy and histologically."

How "well recognized" this is and by whom I do not know; rather than an "idiosyncrasy" I would term this a very serious impropriety in a toxicology study. Failure to confirm gross observations histologically is discussed beginning with paragraph 2 on page 8 of my memorandum to Dr. Finkel of 1/14/77.

IBT in their response (pp. 62-65) attempt to explain this problem but most of their explanations do not make any sense to me. These details at any rate are largely irrelevant since page 95 of the IBT response we find a list of 9 tumors which IBT admits were not originally reported. In addition to these Syntex report another 4 tumors amongst 4 different animals which also were not originally reported by IBT. Even if these 13 additional tumors do not represent the totality of the tumors observed in this study which were not signalled as being observed in the IBT report (and I am not persuaded that they do) these represent an essential concession to our observation that not all tumors noted in this study were originally reported to us.

22. The problem of the gross pathology findings (lesions other than tumors) not being reported to FDA

The IBT response here starting on page 67 admits to the existence of this problem but, they say, "omissions are relatively few and prove to have no material impact on the conclusions within the report."

From the 7 examples cited in Dr. Leventhal's letter, IBT admit this problem is present with 6 of these. IBT, however, make no reference to other animals in this study with exactly the same problem, e.g. animals nos. 9, 11, 20, 24, 54, 66, 71, 108, 119, 148 to cite merely part of these. Conversely, IBT report grossly visible lesions other than tumors without there being any notes on these in such original pathology records as are available, e.g. animals nos. 26, 120, 122, 71, 55, 40, 20, 11, etc.

On page 68 IBT observe that "The types of omitted lesions noted (by them) and their distribution totally lack materiality under the circumstances." I would doubt that such things as hemorrhagic lymph nodes, pneumonia, fatty degeneration of liver, emphysema, hemorrhages in the stomach, hemorrhagic adrenal glands are items that "lack materiality".

IBT further dismisse the importance of these omissions with the observation that "practically all of these tissues....were examined histologically... This was done for all animals listed with the exception of only one observation in animal 25 and animal 59." This statement cannot be true: in the first place, there is a third exception (see the IBT list on page 67) for the lung of animal 86. Secondly, it is not true because the bladder of animal 86 (listed as having been examined histologically) could not have been so examined since a section of this organ was not prepared - See the Syntex list of such sections.

And, finally, even if the statement were true, the sections examined histologically do not account for the changes observed grossly. Examples:

Animal 25 - hemorrhage of cervical nodes
59 - hemorrhage of lymph nodes
- enlarged thyroids
113 - necrosis of the liver
122 - fatty degeneration of the liver
143 - swollen and hemorrhagic mesenteric lymph nodes

These are merely a few instances where there is no accountability of changes observed grossly on microscopic examination.

In conclusion, I would say that even if microscopic examinations were justifiable for omissions of gross findings in the IBT report (and they are clearly not justifiable) a substantive portion of the recorded results of such examinations does not account for the changes observed grossly.

The IBT conclusions here (their page 68) "...in a scientific sense virtually all of the findings were accounted for in the report," is simply not true by an extremely wide margin.

23. The problem that IBT knew their report would be submitted by Syntex to the FDA in support of an NDA

IBT in this section of their response (pp. 69-70) get on their high horse and assume a posture of wrathful and self-righteous indignation: "disturbingly biased phrases", "uninformed aside", "provocative phrase", "inexcusable", "unfounded allegation", "reprehensible", etc.

Following the use of such epithets they assert: "In the vast majority of cases IBT conducts its research in terms only of the protocol without specific knowledge of the many different ways the reports may or may not be used"..."IBT is usually not privy to the client's plans and intentions" ...."In the case of this study for Syntex, IBT recalls no disclosure by Syntex to IBT that the report would be submitted to FDA. IBT was definitely not aware of its being submitted..."

Elsewhere here IBT asks: "What did the author (of Dr. Leventhal's letter?) know about what IBT knew or did not know in relation to Syntex' use of the IBT report? Does the FDA have even a shred of evidence concerning the matter?"

As our "shred of evidence", I would merely append here a copy of a letter we have from IBT's files (note the inspector's initials on it). The letter is self-explanatory.

At the bottom of page 69 of their response IBT observe: "The report is the property of the client. The client may even throw it away." I suspect that the IBT client in this case, Syntex, may now wish it would have done precisely that.

24. The problem with the incorrect, misleading and false statements made by IBT

IBT's response here (page 71) is that there are no "material" errors and omissions, that such errors are "minor" and "meaningless" and that "there is little point in either the FDA or IBT going down that road and in the end spending unaffordable time debating (these)."

IBT is further of the opinion that what they submit in their responses "factually establish(es) that the (IBT) report was acceptable and that it casts no observable shadow."

25. The problem of the reported body weight means not reflecting those found in IBT's records

IBT's response here (pp. 72-73) acknowledges such differences but attributes these either to "rounding off numbers" or to "transcription or clerical errors." What are some of these differences listed by IBT?

405 va. 400
389 vs. 392
254 vs. 242
247 vs. 233
433 vs. 429
440 vs. 431
419 vs. 435
261 vs. 248

As is their wont here, they address merely the examples given by us and not any other differences which they may have encountered through their own audit of the data.

Just to give one such example out of many others that could be presented here:

The internal IBT records disclose for the weighing of 1/30/70 (said to be that for the ninth week) the following means in grams:

Control -	males	429
	females	270
Low level -	males	433
	females	267
Mid level -	males	440
	females	267
High level -	males	419
	females	261

The IBT report reveals the following weights for the ninth week:

Control -	males	364
	females	238
Low level -	males	375
	females	231
Mid level -	males	374
	females	230
High level -	males	367
	females	221

The IBT report also reveals that for the 11th week the means for the control males and females were identical with those in the internal IBT records for the 9th week, i.e. 429 and 270 gms. respectively, as given above. What were the other values reported for week 11?

Low level -	males	429
	females	263
Mid level -	males	431
	females	256
High level -	males	425
	females	248

Rounding-off errors? Transcription errors? Clerical errors?

I repeat, this was merely one example out of the 33 weighings reported by IBT. In their response they did not comment on this.

26. The problem with the missing pituitary gland weights

IBT concede (page 74 of their response) that the weights of the pituitary glands were omitted from the report. They ascribe this to "an oversight." They also state that this organ is "difficult to always remove in toto." By their own admission they apparently missed "removing it in toto" (44-26) x 100/44 = 40.9% of the time for which "not always" would be a euphemism.

The statistical analysis to which IBT refer here (given in more detail on their page 87) is, as with most other such analyses of variance carried out by IBT on this and other studies, completely useless. This had been pointed out to them repeatedly by us since April of last year. The sense in which this is useless is that the type of analysis carried out by them does not account for the ordering of the treatment levels. According to their method, both the following situations would give identical answers:

	Hypothetical Scores	
	Situation A	Situation B
Control	0	3
Low level	1	0
Mid level	2	2
High level	3	1

when it is clear that under Situation A a dose-related effect is apparently present while in Situation B this is not the case.

As a consequence of their erroneous statistical analyses (and this is true of practically anything they analyze, not just pituitary gland or other organ weights) they can simultaneously signal as "significant" a situation where no toxicologically useful information is indeed significant and class as "non-significant" a case where in fact such significance could be present and demonstrated by the use of a proper method of analysis.

27. The problem with the discrepancies on gross pathology findings between the IBT report and their own internal records

Here IBT admit (paragraph 1, page 77) that: "It should be made clear that...not every gross observation ended up in the Appendix (submitted to the FDA)." This certainly was not "made clear" in the original IBT report submitted to the FDA. They then discount this admission by stating: "However, the inclusion of this information does not change the conclusions of the report," as if this is a justification of such omission. They state further that: "It does not detract from the finding that the stomach was the target organ and the principal site of the toxic effects of the drug." This is a complete non-sequitur; the issue is here that if not every gross observation is reported, how is a reviewer to satisfy himself or verify that the stomach is the only such principal site of drug action?

The previous page of IBT's response (page 76) deals with the other side of this coin: the case where the report submitted to the FDA refers to lesions which do not appear in internal IBT records. There are several problems with this -

a) IBT state (paragraph 1, page 47): "Gross findings in Appendix II of the report (submitted to the FDA) include notations which were made on the cage cards for the individual animals; therefore some of these findings were never noted on the necropsy log." I have problems with the word "therefore" here. Appendix II which lists the lesions animal-by-animal in numerical order could not have been prepared prior to the necropsy log being completed which lists the gross lesions in chronological order (more-or-less) of dates of necropsy. It would follow then that the explanation offered by IBT here - that the "omissions" from the necropsy log were balanced or justified by the "inclusions" in the Appendix - is not likely the "right" explanation.

b) we have been persuaded by both Syntex and IBT that the necropsy log contained the observations from the cage cards (see paragraph 2 on page 16 of the IBT response) and on the "fidelity of other data transcribed (to the necropsy log) from other sources which happen to be unavailable" (see bottom of page 23 of the IBT response). If so, how could the Appendix in the report contain information (from cage cards) which is not present in the necropsy log? My own suspicion here provides a different explanation which seems far more likely to me: such information in the Appendix (submitted to the FDA) sprang forth largely if not entirely from the head of whoever compiled that Appendix - Mr. Plank, in all probability. Note that this situation is quite similar to that of the TBD animals discussed here in subsection 16, but additional animals were involved: from the little table on page 76 of IBT's response only one animal (129) is a TBD animal; the others (55, 87, 94, 99, and 101) are not in this category. We are saying, therefore, that what appears as a deception for the TBD animals is not limited merely to those in that category - see also subsections 13 and 18 here.

c) In their table on page 76 of their response dated 11/11/76 IBT imply that what the Appendix II of their report contained for the six animals listed there was "from cage cards." But how can they reassure us of this at this time if the cage cards are no longer available? Have they surfaced in the meantime?

For two of the animals in Dr. Leventhal's list here IBT admit that "for animal 20 (the gross findings) were inadvertantly reported to be those for animal 22" (a "sex mix-up"? - 20 is a male, 22 a female) and that for animal 18 not all findings, including a tumor, were reported.

Paragraphs 2-4 of page 77 in IBT's response are puzzling: "at the time of preparation it was not contemplated by the author of the document that became Appendix II that it would become a part of the report." We were told by Mr. Plank, as remarked elsewhere here, that he himself compiled Appendix II. Is he the "author" of this "document"?

At the bottom of page 77 we read, "The appendix was subsequently adopted by the report writer and incorporated in the report as Appendix II without specifically exploring its genesis with the author." Is the "report writer" someone other than the "author"? The report is said to have been "prepared" by Mr. Philip S. Smith, Assistant Toxicologist, Rat Toxicity, and "approved" by Mr. Plank, Senior Group Leader, Rat Toxicity. Furthermore, the typewritten part of the report (last sentence, paragraph 1 on page 32) clearly refers to this appendix.

28. The problems with not all microscopic findings being included in the IBT report

IBT state here (page 78 of their response) that "It is difficult to understand why this comment was made." They then proceed to discuss just the two examples given in Dr. Leventhal's letter on this issue. Had they carried out a "quality control" type of audit on their own they would have discovered the following discrepancies between the pathologist's notes on microscopic findings and what is given in Appendix II of the report submitted to the FDA:

Animal No.	Pathologist's notes	Appendix II
24	no record of tissues from this animal having been examined microscopically	chronic tracheitis, chronic murine pneumonia
9	no record of tissues from this animal having been examined microscopically	chronic tracheitis chronic murine pneumonia aglandular stomach proteinaceous plug in prostate
25	no record of tissues from this animal having been examined microscopically	chronic murine pneumonia hemosiderosis of the ovary
39	severe focal gliosis	not reported
40	no record of tissues from this animal having been examined microscopically	chronic tracheitis chronic murine pneumonia
48	inflammation of the prostate	not reported
51	severe autolysis	not reported

Animal No	Pathologist's notes	Appendix II
53	autolysis	not reported
54	autolysis	not reported
55	chronic nephritis	not reported
58	no record of tissues from this animal having been examined microscopically	chronic respiratory disease chronic nephritis
59	not reported by the pathologist	necrosis and ulcers of stomach
	inflammation of prostate	not reported
81	not reported by pathologist	ulcers and hemorrhage of stomach
20	tracheitis chronic respiratory disease chronic nephritis adenocarcinoma of mammary gland animal is a female (even though it carries a "male" number)	pneumonia no mention of the mammary tumor animal is identified as mal
83	no record of tissues from this animal having been examined microscopically	chronic tracheitis lymphosarcoma of the lung mucoid plug of the bladder
84	autolysis	not reported
86	not reported by pathologist not reported by pathologist pyelonephritis severe autolysis	chronic respiratory disease erosion and calcification (stomach) not reported not reported
91	severe autolysis	not reported
94	not reported by pathologist	gastritis
98	skin section inadequate (for examination)	not reported
99	no record of tissues from this animal having been examined microscopically	chronic tracheitis chronic respiratory disease pulmonary edema hyperplasia of pituitary gland telangiectasis of adrenal gland
100	not reported by pathologist calculi in urinary bladder lipoma of skin	urinary bladder calcificati not reported not reported

Animal No.	Pathologist's notes	Appendix II
102	pulmonary edema	not reported
	not reported by pathologist	cytoplasmic vacuoles in li
	not reported by pathologist	hemorrhage and necrosis (stomach)
	pituitary hyperplasia	not reported
	telangiectasis of adrenal gland	not reported
	not reported by pathologist	hypervolemia of adrenal gland
109	no record of tissues from this animal having been examined microscopically	chronic tracheitis chronic murine pneumonia
113	no record of tissues from this animal having been examined microscopically	chronic tracheitis chronic murine pneumonia gastritis, hemorrhage and necrosis of the stomach hemosiderosis of the splee (illegible) lesion of kidr adrenal gland hyperplasia
118	not reported by pathologist	necrosis and erosion of stomach
122	not reported by pathologist	hemorrhage, necrosis and erosion of the stomach
	severe autolysis	not reported
140	questionable thymoma	not reported
143	autolysis	not reported
149	severe autolysis	not reported

Notes on animal 20:

a) On page 79 of their response, IBT state (paragraph 2) that animal 20 is actually animal 21, but Appendix II has reference to no results of microscopic examinations whatsoever for animal 21,

b) On page 62 of their response, IBT state (paragraph 3) that animal 20 is a male control and that it yielded no tissues for microscopic examination. If it yielded no such tissues how can the pathologist report (as he certainly did) his findings on the tissues from this animal?

c) On the same page (bottom paragraph) IBT now state that animal 22 yielded no tissues. Yet Appendix II reports microscopic findings on such tissues which are similar to those for animal 20. There is no record to indicate that the tissues of animal 22 were examined microscopically.

d) On page 63 of their response, IBT state: "There were no gross observations of tumors with respect to either animal 20 or animal 22." Yet Appendix II indicates in the "Gross" column an "adenocarcinoma" - generally recognized as being a tumor.

e) On the same page (paragraph 2) IBT say that animal number 20 was actually animal number 21 but this was reported in Appendix II as animal 22; how they can make this sort of determination with any certainty at this time is completely beyond my comprehension.

Notes on Animal 55:

This animal was given as an example in Dr. Leventhal's letter. In their response (page 78) IBT state that the focal chronic nephritis for animal 55 was presented in Table XXIX of the IBT report. But this table on page 53 of the IBT report does not refer to animal 55 or to any other specific animal, for that matter. Interestingly, the table refers to 5 "post-mortem" (i.e. those dying during the study as opposed to those killed at the end of the observation period) males in this group. According to the pathologist's notes these were likely males nos. 51, 53, 54, 55, and 59. Yet according to Appendix II the 5 "post-mortem" males from this group whose tissues were examined histopathologically were nos. 51, 53, 54, 58, and 59.

Notes on Animal 111:

This was the other animal given as an example for this section in Dr. Leventhal's letter. IBT's response on page 78 is that there were no microscopic findings for this animal. This matter was brought up also by Syntex and it was discussed in my memorandum to Dr. Finkel of 1/14/77. The difficulty here is that we assumed that the animal whose number is illegible in the pathologist's notes (but which immediately precedes no. 112) must be animal 111. We arrived at this presumption through a set of deductions: it could not be animal 110 which is listed in Appendix II as having an adenoma of the pituitary gland and had no mammary adenocarcinoma; it could not be either animal 109 or 108 since neither of these is listed in Appendix II as having a mammary adenocarcinoma. I will grant that there is no good reason why the animal with the illegible number in the pathologist's notes should be animal 111 (it also is not signalled in Appendix II as having a mammary adenocarcinoma) but, then, exactly what animal is it?

In summary, by considering the list given above, it appears that the reporting of histopathologic findings by IBT was not entirely accurate. In view of this, IBT's remark (page 78) - "it is difficult to understand why this comment was made" does not strike me as being quite appropriate.

Also note in the detailed list given in this subsection the many instances where autolysis (even severe autolysis) noted by the pathologist as an explicit finding, was not reported even once by IBT. Contrast this with IBT's response (paragraph 2, page 53): "IBT can't believe the report does not fully disclose the generalized experience with autolysis..." And further down in paragraph 3 of the same page: "And regardless of anything else which might be said, it is all too apparent that there was at least sufficient disclosure to make absurd any allegation that the presence of autolysis or lack of histology was affirmatively concealed or withheld."

29. The problem that the incompleteness of the sets of tissues examined microscopically was not reported by IBT

We are being accused here (paragraph 1 on page 79 of their response) by IBT to "exaggerate the impact of a question by including erroneous examples."

With all respect due to IBT, none of the examples given by us are erroneous. Appendix II (submitted to the FDA) contains a list of all organs and tissues for each animal which are implied to have been examined and found to be free of lesions. Yet some of these specific tissues could not possibly have been examined at the time IBT submitted its report since no such sections appear in the list of all sections prepared forus by IBT's client here, Syntex. We have not examined these slides, in fact we have never been priviledged to see them. Syntex has seen these slides and their pathologists have given us a report which alleges to be the sum of total slides form this study given to them by IBT.

From among the 9 animals about which IBT say (paragraph 2 on page 70) that the tissue sets are "unquestionably complete," Syntex' list shows the following deficiencies:

Animal 1 - parathyroid gland
Animal 12- parathyroid gland, skeletal muscle and peripheral nerve
Animal 17- peripheral nerve
Animal 20- uterus, parathyroid gland, eye, and the tissue masses reported as tumorous in the IBT report.
Animal 27- either cecum or colon
Animal 33- esophagus and parathyroid gland
Animal 35- aorta and parathyroid gland
Animal 36- parathyroid gland
Animal 152-esophagus, peripheral nerve and parathyroid gland

Many additional examples are given in the Hein-Gross memorandum of 8/10/76, pages 29-30 there.

And, in case this still does not suffice to make the point here, the following missing tissues are clearly identified in the pathologist's notes, yet not a single blessed one of them is indicated as not having been examined in IBT's report, specifically Appendix II:

Animal		
12	-	lung
28	-	trachea, esophagus
32	-	pituitary gland
36	-	pituitary gland
39	-	pituitary gland
46	-	esophagus, pituitary gland
52	-	pituitary gland
53	-	pituitary gland, adrenal gland, thyroid gland
54	-	pituitary gland
55	-	trachea, lung, esophagus, pituitary gland, adrenal gland
60	-	trachea, esophagus, pituitary gland
66	-	pituitary gland, thyroid gland
69	-	trachea, esophagus
71	-	heart, trachea, lung, liver, esophagus, spleen, kidney, pituitary gland
74	-	heart, aorta, trachea, lung, liver, tongue, pancreas, esophagus, stomach, small intestine, cecum, colon, spleen, lymph node, kidney, urinary bladder, ovary, uterus, pituitary gland, adrenal gland, salivary gland, thyroid gland, parathyroid gland, skeletal muscle, peripheral nerve, spinal cord, brain, skin, thymus
75	-	pituitary gland
77	-	pituitary gland
86	-	trachea, esophagus, pituitary gland, adrenal gland, thyroid gla
94	-	pituitary gland, thyroid gland
100	-	esophagus
105	-	esophagus
114	-	pituitary gland
115	-	pituitary gland
118	-	esophagus, pituitary gland, thyroid gland
140	-	pituitary gland, adrenal gland, (inadequate slide for bone marr
143	-	pituitary gland
149	-	pituitary gland
152	-	pituitary gland

Not only is any of this information withheld from Appendix II, but the same is true for the body of the IBT report where the tables on histopathologic observations given on pages 47 through 56 imply that all animals have had a comparable number of tissues examined histopathologically. It is amply evident from the lists given above that this could not possibly have been true. A reference to these tables is made in paragraph 3 of page 79 of the IBT response.

The paragraph before the last on page 79 is a patent lie: "Whatever 'lack' of information may now be suggested the same lack was obvious at the time the report was accepted." Inasmuch as Appendix II (the detailed animal-by-animal list of tissues examined microscopically which was submitted to the FDA) does not give the slightest hint on all the missing tissues identified above, and inasmuch as all this information was obtained by the FDA only pursuant to an inspection and an examination of internal records of IBT never previously submitted to the FDA, the value of the allegation now being made by IBT becomes self-evident.

I would class the rest of the IBT response here (pages 80 through 82) as being completely irrelevant to the main thrust of this subsection. I was intrigued, however, by the fact that the second paragraph on page 81 carried a reference to "major organs." Having been trained as a pathologist and having worked for many years as such without once having heard this notion - major organ - I wonder just what organs IBT considers as "major," presumably as opposed to "minor" ones.

Further in the same paragraph we read: "of the target organs (the stomach and kidneys) tissues from only two of the former and one of the latter were missing. Nowhere in the IBT report is there any kind of a hint in any of their conclusions that the kidney may be a target organ of the drug tested. I was also unable to find in the IBT report submitted to the FDA that two stomach (tissues) and one kidney (tissue) were missing.

30. The problem with IBT not reporting the inadequate eye sections reported to them by their own pathologist

This problem is similar to the one in the subsection just preceding this one - Appendix II implies that all eye sections were adequate for examination and that the optic nerve was examined in each case. This was obviously not true as can be ascertained from the notes kept by IBT's pathologist. Fortunately, however, despite an entire page of comments in their response here, IBT do not dispute this issue.

31. The general problem with the competence and performance of IBT's pathologists

In their response here, pages 84-85, IBT appear to be chagrined over our criticism. They say that our "attack" on their pathologists "is obviously premised upon the prior enumerated IBT deficiencies which have already been refuted."

If such deficiencies as were enumerated in Dr. Leventhal's letter can be thought to have been successfully refuted in this entire IBT response, I would be the first to apologize to IBT's pathologists for the assessment made here; however, if there is some doubt as to whether there has been an effective refutation process here, I would tend to let our criticism stay in place.

M. Adrian Gross

Encl.:- Letter Syntex/IBT, 11/8/71

November 18, 1971

Dr. Joe Calandra
Industrial Bio-Test
1810 Frontage Road
Northbrook, Illinois

RH-792

Dear Joe:

I am returning herewith for corrections and additional data a report prepared by your organization on a chronic toxicity study in rats with Syntex compound RS 3540.

I am very disturbed at the unsatisfactory nature of this report. It contains a large number of errors, discrepancies and omissions of data which I have indicated in red throughout the report. Data omitted was clearly requested in the original protocol (copy attached).

From past experience I am convinced that the report would be rejected by regulatory agencies in the U.S., U.K., Canada and Germany.

Would you please see that the report is corrected and returned at the earliest.

Very truly yours,

Robert Hill, Ph.D.
Director of Toxicology

RH:lc
Enclosures

MEMORANDUM

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

TO : Dr. Marion J. Finkel,
HFD - 100

DATE: February the 22nd, 1977.

FROM : M. Adrian Gross
HFD - 108

SUBJECT: The 22-months rat study on Naprosyn carried out by Industrial Biotest (IBT)

The following is in response to your request that I comment again on the subject under reference and that I summarize the principal problems involved here:-

It seems to me that two main difficulties exist with this study:-

I) The unavailability of a substantial part of the original records of observations collected while this work was in progress;

II) The apparently vast amount of false information presented in the IBT report on that study.

The following are some elaborations on these problems:-

I) The lack of records

The significance of this is twofold:-

a) it may represent a violation of a published regulation; see Sec. 505(j)1.

b) its impact (materiality) is that without such records no-one can verify for the purpose of authentication the reliability of the data reported by IBT to Syntex which IBT knew (before the submission of their final report) Syntex would transmit to the FDA in support of an NDA. This becomes even more important for studies like the one under discussion here, where the quality of the reported data, judging from whatever records are available, is extremely undependable.

As mentioned in our memorandum of 8/10/76 appended to the Establishment Inspection Report, the following were said by IBT to be unavailable:-

a) all the cage-cards which are represented by IBT and Syntex to have carried observations made both before and after the death of the animals on test;

b) a great part of the body-weight records collected periodically;

c) all original records of hematology determinations;

d) all original records of blood chemistry determinations;

e) approximately 80% of the original gross post-mortem observations.

Even some "non-original" (derived) records kept by IBT, such as their "necropsy log" do not contain pertinent data for each and every animal alleged to have been on test.

II. False information

This main problem has several distinct aspects. One may think of "false" information submitted in a report as anything that can be shown to be different from what is recorded as an "original" observation. For example:-

The IBT report states (page 60) that blood samples were "taken from (animals in) each group after 22 months of feeding...". On their next page, however, they report the hematologic values of animals nos. 13 and 31 neither of which survived to 22 months:- the IBT necropsy log indicates animal 13 to have died on 3/26/71 and animal 31 on 10/5/70 (the study was initiated on 11/25/69). Syntex themselves, on the basis of reviewing original body-weight records, indicate animal 13 to have died by 16.4 months and animal 31 by 10.4 months into the study, and the same can be found in an IBT communication to us dated 11/11/76. Exactly the same is true of other clinical laboratory procedures such as blood chemistry determinations - see IBT report pages 65 and 66.

In these rather simple examples mentioned just above we are being offered, without question, "false" information. Yet I shall not concern myself here with this sort of thing which does not appear to me to be of any material significance in the sense that it can substantially affect the FDA review of this study.

Amongst the problems that I would view as "material" (in the sense described above) I would class all those where information conveyed to us in the IBT report tends to present the results of the study in a markedly different light than such results were in actuality. Their "materiality" can be judged from the answer given to a single question:- had we known the truth about these results, would we have reached the same final decision as we reached originally - that this study was of an acceptable quality ? It is important to realize that such "material" false items of information can be either of commission or omission.

I have selected here three separate (though with some impact on each other) material issues of this kind as being the most important in my judgment with respect to the problem of false information. They are, by no means, all issues related to this. Although each of the three will be discussed separately in greater detail below, I may simply sketch their nature rather briefly here:-

The First Issue deals with the fact that a very large number of dead animals on which at most a cursory post-mortem examination was made by probably inexperienced and unsupervised "animal room technicians" and for which virtually no gross lesions were indicated, was not signalled in the IBT report submitted to the FDA. This omission, by itself, is highly material in the sense described above:- had we known this at the time of the original review, our evaluation would have been that the study was of a totally unacceptable quality.

This false information (by omission) has apparently been reinforced by a

purposeful act of commission:- it seems to me that the data submitted in the IBT report for this particular set of animals was not merely false but actually falsified with likely intent to deceive.

The Second Issue deals with the vast amount of false information contained in the IBT report on merely a subset of the pathology data - that part which is limited to the tumors elicited in the animals on test. The reasons for the materiality of this issue are given in greater detail below where this issue is discussed at greater length; such reasons are referrable to the fundamental importance of this particular subject.

The Third Issue addresses the apparently hopeless confusion on the identity of the animals on test. Again, in the sense that this very serious problem was not disclosed or even alluded to in the IBT report (which implies that the identity of each animal was known at all times) it can be viewed as an item of false information, an indirect misrepresentation of the true state of affairs at the time this study was carried out. The materiality or importance of this difficulty is discussed in greater detail when this subject is reached here.

Finally, the last section of this memorandum contains a note on the tumorigenicity (carcinogenicity) of Naprosyn as judged from the results of this particular study.

False Information - First Issue - The TBD animals.

This problem concerning the animals marked TBD as well as its significance (materiality) was discussed at some length on pages 12-15 of my memorandum to you of 1/14/77. To recapitulate its salient features here:-

1. The term "TBD" used in the IBT necropsy log with reference to dead animals is an acronym which, we were told by IBT at the time of the inspection, stands for "too badly decomposed".

2. We are being informed separately by Syntex and by IBT that this term does not necessarily imply "advanced post-mortem autolysis" although it may do so. Other "factors" governing its use are "the animal room technician's signal to indicate that after weighing all factors, he made the decision to necropsy the animal himself. Those factors include autolysis, time of day, day of week, numbers of dead animals, etc., but autolysis, to be a factor, does not have to be in an advanced state." (Quoted portion from paragraph 1, page 52 of IBT's communication to FDA, 11/11/76). What this says to me is that technicians not ordinarily conducting necropsies decided by themselves to embark on this task whenever they perceived certain "factors" to be at a given state; autolysis, was merely one such factorumongst others.

3. While advanced autolysis is a justifiable and accepted reason for carrying out merely a superficial examination of a carcass, autolysis of less than an advanced state is not such justifiable a reason for this and neither are any of the other "factors" mentioned above.

4. What is the scope of this problem ? Appendix A gives the details on this:- there are 55 entries of TBD in the necropsy log for animals in this study but these represent only 54 separate animals since two TBD entries are made on two separate dates for a single animal - no. 136.

These 54 animals represent almost one-half (46.55%) of the 116 animals in the study which were not killed at the end of the 22-months observation period; if we count merely the 133 animals accounted for in the IBT necropsy log and subtract the 44 animals killed at 22 months, the 54 TBD animals become 60.67% of all animals dying in this study and accounted for. This is hardly a negligible proportion, or one that may be regarded as unavoidable in the usual, adequately run, chronic toxicity test.

5. As can be seen in Appendix A here where all the TBD animals are listed individually, only one of these (No. 146) was indicated in the IBT necropsy log as having any kind of grossly visible lesions at the post-mortem examination - this was a tumor in this case. Yet as many as 48 out of these 54 TDD animals are listed as having some kind of gross lesion (pneumonia or other lung afflictions for the most part) in Appendix II of the IBT report which was submitted to the FDA.

6. We are being "reassured" by IBT (see their 11/11/76 communication to FDA, paragraph 3, page 23) that the necropsy log contained data transcribed from other sources and by Syntex (Vol. I, paragraph 2, page 48 of their current submission in response to our NOH) that such transcription was made "without error" and that "it is highly probable that the cage card transcription (to the necropsy log) was equally accurate". It follows that it is not likely that gross pathology information on as many as 48 animals could have existed without this being transcribed to the necropsy log.

7. If so, the gross pathology lesions for these animals - absent from the necropsy log but entered into Appendix II of the IBT report submitted to the FDA - must be false.

8. Page 15 of my memorandum to you of 1/14/77 also discusses the possibility and likelihood that this kind of information was not merely false but probably falsified with deliberation and intent to deceive.

False Information - Second Issue - The matter of the tumors elicited in the study

In the area of pathology, the most significant aspect of any long-term experimental toxicity study, one of the most important features is the risk of neoplasia or tumor induction. This is so since most chronic or long-delayed effects due to a new drug can conceivably be detected in an exposed human population and, if so detected, the possibility of arrest or even reversal of such undesirable effects is at least possible upon cessation of exposure. However, this is not generally true of neoplastic conditions:- these can be latent for a much longer period of time (several decades) and they are difficult to associate with any specific etiologic agent in epidemiologic studies. The reason for this is that such conditions are generally very rare even when the risk is increased significantly or many-fold over the "normal" background level; a contributory aspect to such difficulties is that, unlike experimental animals, other agents to which humans are being exposed may be responsible for certain observed increases in the incidence of neoplasia. Most important, however, even when such agents are nevertheless detected as causing a carcinogenic response in humans, the arrest or reversal of this type of response is not attainable for most kinds of neoplasia; neoplasms or tumors are defined as progressive disturbances of uncontrolled cellular multiplication or tissue growth.

For these reasons, the matter of tumors elicited in any experimental "safety" study attains extraordinary significance; indeed, it can be considered to be the most important aspect of any long-term experimental animal study.

A reading of the IBT report on its study with Naprosyn results in a conclusion that no problems of any kind were experienced on this particular aspect - the tumorigenic potential of the agent on test. Indeed, the report on this study was found upon initial review in the FDA to be such that a conclusion of "safety" from this point of view was reached and the drug was approved for marketing.

It was only upon inspection of the internal IBT records on this study that the FDA became aware of very serious problems in this area. Many of these problems are of critical materiality since knowledge of each of these at the time of the review would have resulted in this study being considered at least non-acceptable. Other such problems , although not being of critical materiality in the sense described above, are nevertheless of at least peripheral such materiality - this is in the sense that had the FDA had full knowledge of these at the time of review of this study, at least certain questions would have been raised regarding its reliability.

Below is a summary of some of these problems; for additional details as well as for other issues related to this general subject of tumors, please refer to Appendix B of this memorandum.

A. Material problems of great importance:-

1. No original post-mortem observations for grossly visible tumors or lesions likely to be tumors by the prosectors themselves are available (or said to be available) for 130 of the 160 animals in this study. As explained previously, we distinguish between "original" such records made by the observers and "derived" (transcribed) records made by others. It follows that the information presented in the IBT report cannot now be authenticated for each animal by anyone, whether in the FDA, or at Syntex, or even at IBT.

Even the most complete "derived" record of such observations (the IBT "necropsy log") presents important problems:-

a) it has no reference to approximately 27 or nearly 17% of the animals on test and, therefore, no-one can know the date of death for these missing animals, what was the degree of decomposition of their carcasses, or whether they had any grossly visible lesions, let alone what kind of lesions these were;

b) at least six animals are listed as having died on more than one occasion, almost invariably with different information on gross lesions;

c) it is often at variance with the tumor or suspected tumor status presented in the IBT report submitted by Syntex to the FDA.

2. Not all tumors present in these animals - whether such tumors were originaly detected by IBT pathologists during their microscopic examinations of tissues or tumors now acknowledged by Syntex to have been originally missed - were reported initially to the FDA. How large is this problem ? The total number of tumor-bearing animals reported by IBT in their summary on pages 58-59 is only 16. Syntex now admit that animals nos. 77, 100, 20(21), 60, 61, 71, 100, 1, 12, 33, 61, 98, and 10[illegible] (i.e. 13 additional animals) had tumors not originally reported to the FDA. This is not exactly [illegible]

3. There is a very large number of lesions (see details in Appendix B [illegible])

described grossly in such a way that one would strongly suspect the presence of a tumor - externally visible tissue masses, enlarged organs of different kinds, indolent sores, etc.; Yet, only relatively few of these were studied histopathologically. Even when so studied, the gross lesion observed is frequently not accounted for i.e. is it a tumor, a granuloma, an abscess, an ulcer, a hyperplastic or hypertrophic change, a chronic inflammatory reaction, the result of a circulatory problem, etc. As a result of this, one invariably wonders in such cases where absolutely nothing is being said about such lesions after microscopic examination (implying that there were no abnormal findings whatsoever) whether the proper section was collected for microscopic examination.

4. The substantial problem of the TED animals discussed under the First Issue here assumes great significance here due to the superficial examination by inexperienced and unsupervised observers of a large proportion of the animals on this study.

5. The proportion of animals which had any tissues examined histopathologically is well under one-half. In one group of 40 animals, those exposed to the highest level of the agent on test, Naprosyn, no more than 6 or 15.00% had any tissues examined histopathologically. Since no final assessment of tumorigenicity can be made without histopathologic examination of tissues, the importance of this issue is self-evident.

6. The strong evidence for the confused identity of these animals (discussed more amply below under the Third Issue) makes it impossible to be sure what animal had what tumor or tumors, when was any such tumor first observed, when did the tumor-bearing animal die, when did the non-tumor-bearers die, etc., so that a meaningful and informative statistical analysis for latency can be carried out.

I would conclude, therefore, that inasmuch as IBT were silent in their report on all the issues listed above (except no. 5) for which critical materiality can be assigned, and inasmuch as IBT was aware of such problems at the time of preparing their final report which they knew would be submitted to the FDA, the IBT report can be considered as containing misleading and false information.

I should think that Syntex, in not attempting to monitor the conduct of this study while it was in progress or to review the internal IBT data against what IBT reported to Syntex, can be viewed as being negligent in having submitted this false report to the FDA. On the other hand, such views on negligence for a client of IBT's would have to be compared with the kind of monitoring and auditing of the raw data against IBT reports for those testing contracts the FDA itself has with IBT.

B. Problems of lesser materiality:-

1. The discrepancies between the information supplied in Appendix II (the detailed, animal-by-animal account of lesions) of the IBT report and the Summary of tumor findings presented on pages 58-59 of that same report is one of three problems. Its significance lies mainly in assessing the apparently careless way IBT handle the results of their testing and perhaps also in the quality of our own review system. Had a more searching review been made of merely the IBT report (i.e. without the benefit of having internal IBT records

not originally submitted to the NDA) perhaps most of the serious problems listed above would have been detected through an earlier inspection; if so, they could have possibly been corrected or, at least, another similar study at a more reliable institution than IBT could have been undertaken and completed before this NDA was finally approved last March. It may be worth pointing out that a large number of this kind of problem with discrepancies were glossed over by the reviewing pharmacologists and their supervisors even though they were detected by an alert Consumer Safety Officer and by many dozens of other reviewers who are not scientifically trained in pharmacology.

2. From merely the language used by the prosectors at IBT when describing gross lesions it is amply evident, at least to me, that these people were poorly trained and poorly, if at all, supervised by a professional pathologist during the conduct of their duties. At best, this is an issue of only peripheral materiality since the IBT report does not explicitly or even implicitly convey that such supervision in fact took place or that the prosectors were well qualified for such tasks. At its worst, however, this problem can assume critical proportions since it is these prosectors who select the tissue samples or blocks to be examined histopathologically by the professional pathologists; if there is any question on the reliability of these prosectors' performance, the value of the entire study vanishes at least as far as tumorigenicity is concerned.

3. As can be seen in Appendix B here, there are many problems with Syntex' interpretation of these data as set forth in their section on tumors (pp. 458-464 of Volume III, Exhibit 2 of their December 1976 response to our NOH to withdraw approval of NDA 17-581). I should think these are not of great (if indeed of any) materiality here since Syntex cannot have any first-hand information on the data generated in this study anymore than we have, or, for that matter, than the man in the moon. Still, a number of the conclusions reached by Syntex have been questioned here in Appendix B.

<u>False Information - Third Issue - The confused Identity of the test animals.</u>

The matter of the identity of the animals in this 22-months rat study carried out by IBT is, to put it rather bluntly, in chaos.

Why is this a material issue ?

I know of no experimental long-term study in animals such as this IBT effort, which has been found acceptable to the FDA where the identity of the animals on test was unknown or even in grave doubt. This is not without a good reason:-

Any such study has as its purpose not only the demonstration of safety for the agent on test but, particularly with a drug product, the characterization of its potential toxicity for humans. It is largely for this reason that we insist that such studies include a level of the agent tested which is sufficiently high to induce such manifestations of toxicity. But if such manifestations are required, it is also essential that the following be known:-

a) What is the exact time of such indications of toxicity ?

b) [illegible] ?

c) what is their persistence ?

d) what is the variability in such manifestations ?

It is elementary that none of these questions can be answered meaningfully if no one knows for sure which animal is which so that an entire series of observations repeated over the passage of time can be associated reliably with each animal on test. If this were not an important (material) aspect of such a study, it would suffice to expose the animals for approximately two years and then rely entirely on observations collected shortly before death or shortly after their death; it would also not be necessary to distinctly identify the individual animals in each treatment group since only frequency counts of various observations would be appropriate. But this, clearly, would not do.

There are many indications that the identity of the animals in this study was in vast disarray:-

a) the confusion as to the sex of some of the animals - see Appendix B here;

b) the fact that several of the animals are indicated in internal IBT records to have died more than once - see Appendix B here;

c) the discrepancies over the versions of lesions between Appendix II of the IBT report and the summary of tumors noted on pages 58-59 of the same report or between the IBT report on one hand and the internal IBT records on the other hand or amongst different versions of such lesions in different internal IBT records - see Appendix B here;

d) the excessive variability of weights recorded at a given time amongst animals allegedly in one treatment group - see our memorandum of 8/10/76 appended to the EIR;

e) the excessive variability in weights recorded for individual animals with the passage of time - see our memorandum of 8/10/76 appended to the EIR;

f) the contention by Syntex that certain animals identified by IBT with a certain number ought to have been identified with a different number - see Appendix B here;

g) the admission by Syntex that despite their own best efforts they cannot straighten out the identity of some of these animals - the so-called animals with "irreconcilable discrepancies" - see Syntex' Volume III of Exhibit 2 , page 79;

h) the fact that very many animals are indicated to have body-weights recorded at dates subsequent to other dates when such animals are alleged to have died.

In their attempts at resolving or minimizing the difficulties inherent with this very serious problem of identity, Syntex have embarked on what seems to me to be a "gallant" mission. The fruit of their effort here can be found in pp. 53-83 of their Volume III of Exhibit 2 . The center-piece of this section, its main thrust, as it were, deals principally with item (h) above; this strikes me as an interesting exercise in speculative reasoning; but, unfortunately,

not worth very much for two main reasons:-

a) at its best, it is no more than pure conjecture:

b) upon critical examination, this massive Syntex effort entitled "Animal Identity Resolution" has some very serious (in fact, incapacitating) flaws of logic.

A final note on the tumorigenicity (carcinogenicity) of Naprosyn.

Consider the following:-

1) There is no meaningful distinction between the term "tumorigenicity" (propensity of an agent to induce only benign tumors) and "carcinogenicity" (propensity of an agent to induce any kind of tumors) since there is no known agent which upon extensive testing (in a variety of experiments, possibly by different methods of administration, at a variety of levels and in different strains of some species or in different species) can be shown to elicit only benign tumors. It follows, therefore, that any agent which is shown in some experiment to be a "tumorigen" either becomes, by definition, a "carcinogen" or ought to be regarded as such.

2. Let us assume that the 22-months IBT rat experiment on Naprosyn was a perfectly executed piece of work (this does take will-power, I admit) i.e. that all animals were properly identified, adequately examined, etc. Let us focus merely on the female animals in this study and on merely mammary tumors. Let us further assume that the results on mammary tumors among the females were as presented by Syntex in their tumor summary on page 463 of Volume III with one exception:- animal 21 which Syntex believe had a mammary tumor but which IBT state it did not - animal 21 was one of those on which no records (even transcribed such records) exist in the IBT necropsy log, and no one can tell when it died, what lesions it had on necropsy, and, of course, no slides or tissue sections exist for this animal. Yet Syntex maintain that another animal with tumors of the mammary gland (male animal 20) really ought to be animal 21, a female. There are many other reasons for questioning this argument advanced by Syntex, and these can be found in Appendix B here.

If we eliminate, therefore, this finding of mammary neoplasia for animal 21 as being unsubstantiated, but we accept all other mammary tumors alleged by Syntex to have been found, what kind of contrast between control and exposed animals emerges ? There were no animals with mammary tumors amongst the 17 control females accounted for in IBT records, and 8 animals with mammary tumors amongst the 49 exposed females similarly accounted for in IBT records. The probability for this kind of difference under the hypothesis of no increase in incidence for the test group over that in the control group is 0.078, i.e. we have borderline significance here.

If this is judged as not qualifying for "high significance" simply because it does not strictly attain the $p = 0.05$ level usually required for this, additional considerations are in order:-

3. Whether any particular level of significance is or is not reached is a function of two separate considerations:- the magnitude of the difference between two groups being compared and the size of these groups; in general, the smaller this size, the greater the required difference between the two

groups for any given level of significance. For example, the contrast examined above, 0/17 controls versus 8/49 test animals represents a difference between 0.00% for controls and 16.33% for the test animals. If we keep the identical incidences in the two groups but assume now that the groups were two-fold larger, we would have a contrast of 0/34 or 0.00% positive control females versus 16/98 or 16.33 positive test animals. Note that had the identical results (0.00% and 16.33%) been obtained in groups only 1.63 to 1.70 times as large as those that were started in this experiment (20 control females and 60 test females) this contrast would be very highly significant at the $p = 0.0061$ probability level.

4. Alternatively we may assume that three of the test females with lesions suspicious of mammary neoplasia (but which were not examined histopathologically) - these are animals nos. 69 with a subcutaneous lesion (hematoma ?), 107 reported by IBT to have had a mammary adenocarcinoma (disputed by Syntex) and 109 with a subcutaneous mammary abscess, also not examined histopathologically (see Appendix B here) - ought to be given some consideration. If all three of these test animals in fact had mammary tumors the resulting observation (11/49 positive test animals) would, when compared to 0/17 positive controls, be significant at the $p = 0.028$ probability level; if only two of these three animals were positive for mammary tumors, the resulting p value would be 0.039, still highly significant; finally, if merely one of the three animals mentioned here would be positive for mammary tumors, the p value would be $p = 0.056$ i.e. very close to $p = 0.050$.

I would conclude, therefore, that with certain (not unreasonable) assumptions, borderline or high statistical significance on the increase in the incidence of mammary tumors (benign and malignant) had resulted in this experiment.

Because of this, I should think that the view can be entertained that the results of this study indicate Naprosyn to be a tumorigen (carcinogen) and that, as such, it represents an imminent danger to health warranting a prompt removal from the market.

M. Adrian Gross

DETAILS ON THE "TBD" (TOO BADLY DECOMPOSED) ANIMALS - see IBT necropsy log

Experim. Group.	Sex	Animal Number	Histopath. Examination carried out	List of grossly observed lesions in necropsy log	in Appendix II	Remarks
Control	male	4	no	none	pneumonia, lung congestion	
		5	no	none	pneumonia, enlarged thyroid	
		10	no	none	pneumonia, enlarged spleen	
		13	no	none	pneumonia	
		16	no	none	congested lung	
		20	yes	died twice (?)	pneumonia	see Appendix B
	female	22	yes	none	hyperemia, lung, congested, l.n., enlarged adrenal	NTT (no tissues taken) animal
		23	no	none	pneumonia, congested lung	
		26	no	none	pneumonia	NTT animal
		31	no	none	abscess, lung	
Low level (GF I)	male	41	no	none	pneumonia congested lung	
		44	no	none	congested lung	
		45	no	none	pneumonia	
		50	no	none	(?), lung, enlarged spleen	
		56	no	none	pneumonia	
		57	no	none	none	
	female	76	no	none	pneumonia	
Old level (GF II)	male	82	no	none	congested lung	
		85	no	none	pneumonia	
		88	no	none	pneumonia	
		89	no	none	congested and abscessed lung	
		90	no	none	pneumonia	
		92	no	none	pneumonia	NTT animal

Experimental Group	Sex	Animal Number	Histopath. Examination carried out	List of grossly observed lesions in necropsy log	List of grossly observed lesions in Appendix II:	Remarks
id level T II) ontinued	male (cont'd)	95	no	none	abscessed lung	
	female	103	no	none	pneumonia	
		117	no	none	pneumonia, congested lung	
		119	yes	died twice (?)	none	NTT animal
		120	no	none	pneumonia	
gh level T III)	male	124	no	none	pneumonia	
		125	no	none	pneumonia enlarged spleen	
		126	no	none	abscessed lung	
		127	no	none	tumor-like growth in the lung	
		128	no	none	pneumonia	
		129	no	none	ulcers of stomach	
		130	no	none	abscessed lung	
		131	no	none	pneumonia	
		132	no	none	none	
		133	no	none	pneumonia	
		134	no	none	pneumonia	
		135	no	none	pneumonia	
		136	no	none	pneumonia	died 12/6/69 an 2/15/71
		137	no	none	abscessed and congested lung	
		139	no	none	none	
	female	142	no	none	none	
		144	no	none	pneumonia	
		146	tumor only	tumor only	tumor only	NNTT animal
		147	no	none	pneumonia, ulcer, stomach	
		148	no	none	pneumonia	
		150	no	none	abscessed lung	

APPENDIX A (Continued)

Experimental Group	Sex	Animal Number	Histopath. Examination carried out	List of grossly observed lesions in necropsy log	List of grossly observed lesions in Appendix II	Remarks
High level (T III) continued	female (cont'd.)	151	no	none	none	
		157	no	none	congested lung discolored liver	
		158	no	none	pneumonia	
		159	no	none	pneumonia	NTT animal
		160	no	none	abscessed lung	

end of Appendix A

APPENDIX B

TUMORS

CONTROL MALES - Alleged to be on test: Nos. 1-20

Problems:

1. No pathology records of any kind on 5 animals (2, 6, 7, 8, and 15)

2. TBD - 5 or 6 animals (4, 5, 10, 13, 16 and 20) though the last one reported to have died on 8/3/71 (not TBD) and also on 5/11/71 TBD

3. No records on histopathology observations on 12 animals (2, 4, 5, 6, 7, 8, 9, 10, 13, 15, 16, 18)

4. Syntex' list of slides contains no slides for 11 animals (2, 4, 5, 6, 7, 8, 10, 13, 15, 16, 18). Note that they indicate having slides for animal No. 9 but this is not reported as having been examined by the pathologist.

5. a) The IBT Summary of tumors lists only one control male with tumor: No. 20 (21 month[s] on test) with a 24.6 gm adenocarcinoma of the mammary gland.

   b) The IBT Appendix II for animal No. 20 (no time to death given) lists no tumor whatsoever (gross or microscopic) for this male animal.

   c) The histopathology notes refer to animal 20 as being a female with an adenocarcinoma of the mammary gland.

   d) The necropsy log lists animal 20 as having died on 5/11/71 TBD/TDA with no gross lesions whatsoever (approx. 17 months on test) and again on 8/3/71 (approx. 20 months on test) with hemorrhagic lungs, a pituitary adenoma the size of a large pea and two tissue masses: one in the right axilla 24.6 gm and one in the lower left abdominal region (no weight given). Note that the histopathology notes refer to only one tumor for this animal.

6. The necropsy log also refers to enlarged pituitary glands or pituitary adenomas for 4 animals not mentioned in either the IBT Summary of IBT's Appendix II: Nos. 1, 12, 17, and 18. The last one is amongst those with no slides and the first three, although examined, are not mentioned at all as being abnormal histopathologically.

   Syntex' response to the NOH now admits (p. 464, Vol. 37) that the pituitary glands of Nos. 1 and 12 contain adenomas but, for No. 17 they still offer no details on microscopic examination. No additional sections for No. 18 were made and examined.

Comments

Syntex discusses some of the problems with animal 20 on page 459 of their Volume 3. They say "...the date of death identifies this animal as 21," a conclusion that can be no more than a speculation. Because of this, Syntex has improperly chosen to designate animal 20 as animal 21 in their table entitled Tumor Summary on page 463 of Volume 3. As we shall see further below in the section on Control Females, no pathology records whatsoever, no date of death and no slides exist for animal 21. This highly questionable assignation of a tumorous animal whose slides are marked as being No. 20 to become an animal on which it is not known when it died, with what gross lesions, and with what microscopic lesions (there are no slides for it) has a crucial significance as to the statistical analysis of these results.

The fact that "in-life" (ante-mortem) observations for animal 21 include a tumor and an open cyst of the abdominal wall (mentioned on page 459 of Syntex' Volume 3) is unpersuasive: A tumor (unspecified otherwise) is noted in the body-weight records for this animal for the first time on 1/21/71 (at 13.9 months in the experiment), then again on 2/4/71 (14.4 months) on 2/11/71 (14.6 months), 2/16/71 (14.8 months), on 3/10/71 (15.5 months), an "open tumor" on 3/18/71 (15.8 months) and not thereafter (4/5, 4/13, and 4/21/71.

On 4/27/71 "abdominal wall open" is barely discernible for animal 21 and no observation of any lesion is made for this animal on 5/15/71 and 5/24/71. Animal 21 disappears from weight records from 6/1/71 through 7/16/71 (5 weighings only to reappear on 7/27/71 without any observations on lesions. At the next weighing on 8/9/71 it disappeared permanently. It would seem, therefore, that what was observed ante-mortem in this animal can hardly be taken to have been a persistent change lasting until its death.

Much the same is true with other ante-mortem observations of this sort for other animals in this study - see Syntex' notes on page 462 of their volume 3 (last paragraph) for animals 16(15), 38, 47, 63, 113, 145 (144), and 157(152). Syntex' "argument" that the 5 weights recorded for animal 20 between 6/1/71 and 7/16/71 are really the "missing" weights for animal 21 is not a very good one. After all, animal 20 was "dead" as of (at least) 3/18/71; why were not other weights between 3/18/71 and 6/1/71 assigned "wrongly" from animal 21 to animal 20 and why was the weight of animal 21 of 7/27/71 not also "improperly" assigned to animal 20?

Furthermore, if it were true that the five weights from 6/1/71 through 7/16/71 for animal 20 really belonged to animal 21 (as Syntex now speculates) and if it is animal 21 that really had "in-life" tumors which persisted through to its death, why were not such tumors signalled for these five weights "wrongly" assigned to animal 20?

Syntex in their response (page 464, Volume III) address also the pituitary adenoma the size of a large pea noted for animal 20. However, they have no elaboration for this lesion on microscopic examination; they also have no comment for the second grossly visible tissue mass for animal 20 which, as noted above, they choose to assign to it number 21.

I would summarize this entire discussion with the conclusion that although animal 20 appeared to be inexplicably a female, there is no acceptable reason to assign this animal to the female control group as animal 21.

TUMORS

CONTROL FEMALES - Alleged to be on test: Nos. 21-40

Problems:

1. No pathology records of any kind for 3 animals (21, 29 and 38).

2. TBD - 4 animals (22, 23, 26, and 31)
   Animal No. 40 reported to have died a "bleeding death" at a time when no bleedings were carried out.

3. No records of histopathology observations on 10 animals (21, 22, 23, 24, 25, 26, 29, 31, 38 and 40).

4. Syntex' list of slides does not refer to slides for 8 animals: (21, 22, 23, 26, 29, 31, 38 and 40). Note that they indicate having slides for animals 24 and 25 but these are not reported as having been examined by the pathologist.

5. The IBT summary of tumors lists a single animal with a tumor - no. 39 with an adenocarcinoma of the uterus. Yet Appendix II of IBT lists no such tumor for this animal; instead it lists for animal no. 22 an adenocarcinoma with severe inflammation and necrosis at an unspecified site. The internal IBT records list:
   a) for animal 22 no gross lesions whatsoever are recorded since this is a TBD animal.
   b) the pathologist's notes have no reference whatsoever to any microscopic findings for animal 22 for which slides were not prepared.
   c) In their response (page 463, Volume III) Syntex does not present the tumor noted in the IBT's Appendix II in animal 22, although they refer to this tumor on page 459 of the same volume. Although IBT had signalled mammary adenocarcinomas for animals 20 and 22, Syntex apparently chooses to ignore these and maintain that animal 21 had such a tumor - refer to this discussion also under Control Males.

   An examination of the weight tables prepared by Syntex reveals that it is not possible for animal 22 to have been confused with animal 21 since 22 did not die til near the end of the experiment.

6. IBT's Appendix II also lists 3 pituitary adenomas for animals 30, 33, and 35 (all three only grossly but not microscopically); none of these 3 tumors were noted in IBT's summary of tumors on page 58 of their report; the pathologist's notes indicate the pituitary glands of these three animals to have been normal on histopathologic examination; Syntex in their response, on the other hand indicate the pituitary gland of no. 33 to have been an adenoma on microscopic diagnosis but there is no comment on the lesions observed grossly for the pituitary glands of animals 30 and 35.

7. IBT's necropsy log reveals that animal 25 had an adrenal gland hemorrhagic and enlarged 3 times. This animal is not recorded as having tissues examined histopathologically even though slides on it were prepared. In their response, (page 464, Volume III) Syntex indicates no section of the adrenal is available which is consistent with their list of slides for this animal.

LOW LEVEL MALES - Alleged to be on test Nos. 41-60

Problems:

1. No pathology records of any kind for 4 animals (42, 43, 47, and 49)

2. TBD - 6 animals (41, 44, 45, 50, 56, and 57)

3. No records of histopathologic observations for 11 animals (41, 42, 43, 44, 45, 47, 49, 50, 56, 57, and 58)

4. Syntex' list of slides contains no slides for each of the 11 animals listed just above.

5. IBT's necropsy log indicates the liver for animal 53 to have been swollen - this, however, is not elaborated upon in the pathologist's notes for this animal. Syntex in their response do not address this issue in their section on tumors in Volume III.

Syntex, in their response (page 463, Volume III) indicate a lymphosarcoma of a lymph node for animal No. 60; yet there is no such information given in the IBT pathologist's original notes for this animal.

7. IBT's necropsy log indicates a fatty-like growth in the left axilla for animal number 59. No elaboration on this is given by the pathologist in his notes on the histopathologic examination of tissues for this animal. Syntex mentions this problem on page 459, Volume III of their response but on page 463 of the same volume they indicate "no microscopic evidence of neoplasm." What is odd about this situation is where did they expect to find such evidence? Their list of slides for this animal does not include a section of a tissue mass.

8. For the same animal (No. 59) the IBT necropsy log indicates enlargement of the lymph node, thyroid gland, and pituitary gland. None of these is addressed in the pathologist's notes on histopathologic examination for this animal. Syntex, in their response, address this issue on page 464 of Volume III but they also do not have any comments on these three lesions.

LOW LEVEL FEMALES - Alleged to have been on test Nos. 61-80

Problems:

1. No pathology records of any kind for 4 animals (63, 65, 72 and 80)

2. TBD - 1 animal (76)

3. No records of histopathologic examination on 8 animals (63, 65, 72, 73, 76, 78, 79, 80) and of those that were examined No. 71 had many sections missing and No. 74 had all but the bone-marrow section missing; this is not indicated in Appendix II of the IBT report.

4. Syntex' list of slides indicates no slides for 9 animals (63, 65, 72, 73 except stomach, 74 except bone-marrown, 76, 78 except stomach, 79 except stomach, and 80). Note that animals 73, 74, 78 and 79 are terminally sacrificed animals and, contrary to what is stated in the IBT report, not the full complement of tissues were sectioned and examined histopathologically.

5. IBT's necropsy log lists for animal no. 66 a large fibrous tumor affecting the entire lung whose left lobes weighed 23.9 grams and the right lobes were hemorrhagic and consolidated. This information is not given in IBT's summary of tumors on page 58 of its report or in Appendix II, both of which refer to a mammary fibroadenoma for this animal. The necropsy log has no reference to any mammary tumors for this animal. Syntex in their response on page 463 of Volume III also has reference to a mammary fibroadenoma but not to any lung tumors.

6. Also for animal 66, the IBT necropsy log refers to an enlarged adrenal; this is not being addressed to in the histopathology notes for this animal and Syntex, likewise, has no comment following histopathologic examination of this lesion.

7. An enlarged spleen is reported in the IBT necropsy log for animal no. 70. No further information is given in the histopathology notes for this lesion. No comments from Syntex on this.

8. For animal 69 a subcutaneous lesions (hematoma?) in the center of the back is mentioned in the IBT necropsy log. No further information is given in the histopathology notes for this lesion. No comments from Syntex on this.

9. For animal 77 three separate tissue masses and a subcutaneous hematoma in the center of the back are noted in the necropsy log. Only one of these is reported by IBT in their report and the weight given for it is 155.52 gms. Syntex in their response (p. 459 Volume III) discuss this and point out that the necropsy log indicated the conbined weight of two tumors to be 155.52 gms. and they admit that the left axillary tumor was not reported by IBT. However, they provide no microscopic diagnosis for it (neither did IBT) and they still do not address the subcutaneous lesion seen on the back of this animal.

10. IBT reported for animal 71 a primary (benign) mammary adenoma. Syntex now report (p. 463, Volume III) a metastatic (malignant) mammary carcinoma in the lung of this animal. This is rather unusual - a primary benign tumor can hardly metastasize into a malignant variety at another site. Was an additional primary malignant mammary tumor missed? At any rate, the IBT pathologist missed the metastatic malignant lung tumor in the original IBT report.

11. For animal 64 Syntex reports a pituitary adenoma; this was also missed by the IBT pathologist in the original IBT report.

12. For animal 61 Syntex reports a lymph node lymphosarcoma; this was also missed by the IBT pathologist in the original IBT report.

MID-LEVEL MALES - Alleged to be on test Nos. 81-100

Problems:

1. No pathology records of any kind for 1 animal (96).

2. TBD - 7 animals (82, 85, 88, 89, 90, 92, 95)

3. One animal (87) is reported to have died both on 3/3/71 and 3/11/71

4. No notes on histopathology for 12 animals (82, 83, 85, 87, 88, 89, 90, 92, 95, 96, 97, and 99)

5. Syntex has no slides for 11 animals (82, 85, 87, 88, 89, 90, 92, 95, 96, 97, and 99)

Note that Syntex has slides for animal 83 but these are not reported as having been examined.

6. IBT's Appendix II lists a lymphosarcoma of the lung for animal No. 83 but this is not reported in IBT's Summary on page 58 of its report. This issue is recognized by Syntex but they do not address the fact that there are no entries in internal IBT notes on animal 83 having been examined histopathologically.

7. For animal 84 Appendix II lists grossly a tumor-like growth in the lung but no details on the histopathologic aspects of this lesion are given. Syntex addresses this issue on page 463 of their Volume III but without a satisfactory resolution.

8. The IBT necropsy log mentions an enlarged pituitary gland for animal 98. No report on this lesion is mentioned by the IBT pathologist in the original submission to the NDA. Syntex now acknowledges this lesion to be due to a pituitary adenoma.

9. The pathologist's notes indicate a lipoma for animal 100. This was not reported by IBT either in the Summary on page 58 or in Appendix II, a fact acknowledged by Syntex in their response (see their pages 460 and 463 of Volume III).

10. The pathologist's notes indicate animal 102 to be a male but Syntex' list of slides indicates this animal to have female reproductive organs.

MID-LEVEL FEMALES - Alleged to be on test Nos. 101-120

Problems:

1. No pathology records of any kind for 2 animals (101 and 116).

2. TBD - 4 animals (103, 117, 119, and 120)

3. No records of histopathologic observations for 9(10) animals (101, 103, 108, 109, 110, 111, 113, 116, 117, 120) though either 108 or 109, or 110 or 111 with an illegible number is probably available. Syntex, in their response (page 450 Volume III) assert that the animal with the illegible number is likely No. 110. This cannot be demonstrated, however, since this particular animal is noted as being a "P.M." animal (meaning it died during the study) when No. 110 is indicated as being a terminally sacrificed animal in IBT's necropsy log; also No. 110 is not indicated in IBT's Summary of tumors as having a mammary tumor. It is not established that this could be either numbers 109 or 108 (both "P.M." animals) since neither of these are indicated as having mammary tumors as is the case with the animal with an illegible number. Additionally, 108 had no slides prepared from its sections according to Syntex' list.

4. Syntex' list of slides lists no slides for 7 animals (101, 103, 108, 111, 115, 117, and 120). Note that slides were prepared for No. 113 but there are no records of these having been examined. Also note that while the vast majority of animals with essentially full complements of tissue sections collected for histopathology examinations have between 5 and 6 slides which include all such sections, for animal 102 there are 11 such slides with a large number of tissues duplicated: eye, l.i., skin, urinary bladder, uterus, liver, spleen, kidney, heart, lung, tongue, l.n. adrenal gland, bone and bone marrow, while others are triplicated: skel. muscle, brain, spinal cord, aorta, stomach, pituitary gland, etc. A likely reason for this oddity can be found in problem No. 5. below.

5. Two animals (102 and 119) are recorded in the necropsy log to have died more than once:

   a) animal 102 (a female) is said in the necropsy log to have died on 6/24/71 with no grossly visible lesions but with a grade 4 state of decomposition of its carcass. On 7/30/71 the same animal is recorded to have died with a grade 3 such state, with pneumonia (scored as +3) and a hemorrhagic stomach. It is also noted to be a "missexed female." In the histopathology notes, this animal is classed as a male even though, as seen above in problem 4, Syntex' list of sections from this animal indicates the presence of uterus and ovaries. On 7/30/71 (both on another page of the necropsy log and after some other 8 animals are said to have died both before and after 7/30/71) animal 102 is listed as having died but this time it is indicated to be a male. There is no information on the degree of decomposition of its carcass and no gross lesions whatsoever are reported.

   b) animal 119 is recorded as having died only twice: on 6/2/71 when it was listed as TBD/NIT (meaning "too badly decomposed, no tissues taken (for histopathology)") and again on 8/18/71 when its lungs are indicated as being hemorrhagic. Fortunately, however, this animal retained the same sex at each of its two recorded death dates.

6. The IBT Summary of tumors on pages 58 and 59 of its report has Animal 107 indicated twice as bearing a mammary adenocarcinoma: once on page 58 and once on page 59; did this animal have two such tumors? Yet IBT's Appendix II lists a mammary adenocarcinoma for number 110 which does not appear in IBT's Summary table. Syntex in their response (page 463 Volume III address this problem and they also give us their "solution": The Summary Table entry for 107 is a "mistake" and the Appendix II note for 110 is "correct."

They are not enlightening however as to just how they arrived at this determination (they were not the originators of the actual data in this study) and if they know what animal had what tumor now, did they not know it at the time their report was submitted to the FDA? If they did have such knowledge, why was this not transmitted to the FDA before December 1976?

7. IBT's Appendix II indicates animal 109 to have had a pituitary adenoma on mere gross examination. Neither Appendix II nor the histopathology notes (not submitted to the FDA) mention the character of this gross observation after microscopic examination. Even Syntex' response (page 464 of Volume III) although recognizing this problem, is not helpful in elucidating it since no comments are made even there on the microscopic details of this lesion.

8. IBT's necropsy log indicates animal 109 to have had a subcutaneous mammary abscess which could turn out to be a suppurating tumor on microscopic examination. There are no details being given on this lesion after microscopic examination either in the original internal IBT records on histopathology findings, or in the Syntex response and this lesion is not signalled in the IBT report submitted to the NDA by Syntex.

9. Animal 102 (although mentioned nowhere by IBT (in the Summary of page 58 of their report, in Appendix II of their report or in the histopathology notes) to have had a tumor of the pituitary gland or even a grossly observed lesion at this site, is signalled by Syntex in their response (page 464 of Volume III) to have had such a lesion.

HIGH LEVEL MALES - Alleged to be on test Nos. 121-140

Problems:

1. No pathology records of any kind for 3 animal (121, 123 and 138).

2. TBD - 15 animals (124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, and 139)

3. No records of histopathologic observat for 18 animals (121, 123, 124, 125, 126, 127, 128, 129, 130, 131 132, 133, 134, 135, 136, 137, 138 and 139)

4. Syntex have no slides for the same 18 animals as in (3) above.

5. Two animals are recorded as having died twice in IBT's necropsy log:

a) animal 122 is recorded as having died on 7/30/71, with a grade 3 decomposition of its carcass, fatty degeneration of the liver, lungs pneumonic (+3) and hemorrhagic stomach; seven entries subsequent to this after other animals are recorded as having died both before

*one animal (136) died both on 12/8/69 and 2/15/71

and after this date, animal 122 is recorded again as having died with no decomposition grade of its carcass and with no observable gross lesions.

b) animal 136 is recorded in the necropsy log as having died on 12/8/69 with the notation TBD/TDA and again more than 14 months later on 2/15/71 also with the notation TBD/TDA.

6. Animal 127 is not listed in IBT's Summary of tumors on pages 58-59 of their recport as having any tumors. Yet Appendix II of the IBT report lists a tumor-like growth in the lung of this animal in the "gross" column only. This feature is not indicated for the necropsy log entry for Animal 127 or in the IBT histopathology notes. It is addressed, by Syntex in their response (page 463) but without a satisfactory resolution.

7. Animal 140 is reported in IBT's Summary of tumors on pages 58-59 to have had a lymphatic tumor weighing 4.65 gm. This observation does not appear in IBT's Appendix II. The necropsy log refers to a "lymphatic tumor" for this animal, though how a prosector can decide at the gross post-mortem examination that any lesion is a "lymphatic tumor" is beyond my understanding. The pathologist's notes on microscopic examination of lesions has no reference whatsoever to a "lymphatic tumor" but instead he has entered for this animal a "thymoma" with a question mark. This issue is presented in the Syntex response on page 463 of their Volume III but only superficially so (without the details given here) and, of course, with no satisfactory resolution based on additional microscopic examination of this lesion.

HIGH LEVEL FEMALES - Alleged to be on test Nos. 141-160

Problems:

1. No pathology records of any kind for 5 animals (141, 145, 153, 155, and 156)

2. TBD - 11 animals - 9 TDA (142, 144, 147, 148, 150, 151)157, 158, 160)
1 NATT(146)
1 NTT (159)

3. No notes on histopathology for 16 animals (141, 142, 144, 145, 146 (except tumor), 148, 150, 151, 153, 155, 156, 157, 158, 159, and 160)

4. Syntex' list of slides does not include slides for any of the 16 animals in (3) above. Note that Appendix II of IBT's report submitted to the FDA does not indicate that only a tissue mass was examined histopathologically for animal 146.

5. For animal 149 IBT's Appendix II lists a tumor as well as hematopoiesis for the spleen. IBT's Summary of tumors on pages 58-59 of their report neglects this tumor even though it was present in the histopathology notes. Syntex addresses this issue on page 463 (Volume III) of their report but then states that no tumor of the spleen is present, thus in effect disagreeing with the IBT pathologist.

6. For animal 145 IBT's Appendix II lists a pituitary adenoma grossly. This is not presented in IBT's Summary of tumors on pages 48-49 of their report. The odd thing about this is that there are no pathology records for this animal (no entry in IBT's necropsy log), no histopathology observations, and no slides.

7. Animal 152 is recorded in the IBT necropsy log to have had mesenteric lymph nodes swollen 100 x normal or more (!?) and the spleen enlarged (+2). Neither of these lesions are elaborated upon in the IBT pathologist's notes for histopathologic findings for this animal. Syntex refer to this problem on page 464 of their Volume III but they are no more helpful here.

8. Animal 143 also is recorded in the IBT necropsy log to have swollen mesenteric lymph nodes but this is not presented in Appendix II of the IBT report, or in the pathologist's notes. Unlike the case in (7) above, Syntex does not recognize this problem.

9. Oddly enough, Syntex in their response (page 464, Volume III) indicate an enlarged pituitary gland and lymph node for animal No. 153 but I could not find any kind of entry whatsoever anywhere in IBT records or reports for this animal.

10. Much the same is true for animal 158 where Syntex reports an enlarged pituitary gland (page 464, Volume III) when all I could find in IBT's necropsy log was that this was a TBD/TDA animal which died with no lesions whatsoever recorded. Does Syntex have any special information on this animal and, if so, what is its source?

FOOD AND DRUG ADMINISTRATION

TO : Associate Director for New Drug Evaluation (HFD-100)

DATE: FEB 23 1977

THRU: Director, Division of Oncology and Radiopharmaceutical Drug Products (HFD-150) W. Young MD

FROM : Manfred M. Hein, Pharmacologist, HFD-150

SUBJECT: Identification of Misstatements in Naproxen Matter

At the February 17, 1977 meeting Dr. A. Gross and I were assigned the task of identifying a few issues in which there exists a substantiatial misstatement of facts between the report issued by IBT regarding the 160 rat 22 months toxicity study, dated January 4, 1972 (submitted by Syntex to FDA as part of INDs 5,281; 7,428 in 1972 and NDA 17-581) and findings resulting from the investigation at IBT in June of 1976. The information is to be used for the formulation of the FDA reply to the company response of December 14, 1976 to the Notice of an Opportunity of a Hearing (FR 41 #201 October 15, 1976) in the matter identified also as Docket 76N 0411.

I hope the enclosed will accommodate the need at this time.

Manfred M. Hein

Manfred M. Hein

ISSUE	IBT REPORT	SYNTEX RESPONSE TO NCH	FDA POSITION
The identity of each animal is paramount to a correlation of gross, histological and other findings including (but not exclusive of others) the administered dose, in vivo observations of behavior, weight data dates of death, sex and clinical pathology. The identity is essential for interpretation of scientific findings as they relate to safety.	The original IBT is limited to group mean values without measures of central tendency for any parameter except as follows: Hematologic data on survivors to 22 mos. Clinical chemistry on survivors to 22 mos. Organ weight data on survivors to 22 mos. (The above is not available even in group data for animals dying prior to 22 months.) Table listing the tumor findings of specific animals. The Gross and histopathology summary sheet (Appendix II)	"Reconstruction" of the IBT study using available raw data, the report and conjecture. Supplementation by additional pathology data by Dr. Richter from stored carcasses.	32 wght record sheets organ wght data necropsy logs pathology reports 30 autopsy records } indicate inconsistencies to date of death, identity of animal, specific findings of IBT report. See Hein/Gross report 8/10/76. "Reconstruction is unable to interprot all inconsistencies, is not based entirely on facts, but includes suppositions. Done by Syntex not persons doing study. (See review of 8/30/76.) Only individual data on animals dying before 22 months. Identity of stored tissues in question.
"Group findings" rather than individual data is available without mixups.	IBT on 11/12/76 stated that study was designed to generate group not individual data.	Intent to present group data only.	Animal mixup between #20 & 21. Respectively designed to be male & female found by histologist to be mixed up. Terminal sacrifice at 22 mos. limited to 1 female rat of high dose group is inadequate to characterize "group."

Observations of general conditions and behavior (clinical observations).	Protocol provided for daily observations of general conditions and behavior. It further provided for "Reporting quarterly and at termination".."An assessment of toxic effects, the general behavior and condition of the animals, body wghts, food consumption, fatalities, laboratory findings, gross and histological pathology, organ weights and organ/body weight ratios". Protocol was part of submission. The IBT report is SILENT on observations of general conditions and behavior. There were no interim reports.	Syntex prepared protocol for study. Protocol is included in "reconstruction" of IBT report. Syntex admits to no animal observations on weekends. The Syntex "Reconstruction" is SILENT on observations of general conditions and behavior.	In vivo observations are an important toxicological parameter. 32 out of a potential 96 weight record sheets were recovered. These contain observations only from 1/21/71-4/27/71 inclusive on general behavior and are limited to "Tumor" "T" (for tumor) "IEI" (inner ear infection) "Dia" diarrhea, "Sore along side of animal" "Open tumor" "?" There are no observations prior to this date or later. Observations are inadequate in content as the "tumors" were not identified as to size, appearance, change with time. No attempt was made to verify them in most cases by gross and histological examination.
	Only mean group weight data without record of range or measure of central tendency is presented. Periodic food consumption by group available in "mean" form.	"Reconstruction" is an attempt to develop individual weight data for each date raw data is available. Syntex has 32 out of a potential 96 records to 'reconstruct' weight history. Records of diet formulation and food consumption used to claim normal good animal husbandry practice.	32 out of 96 potential records of weight are inadequate to reconstruct the body weight history. No observations are included prior to 1/20/70 (about wk 8) or for periods of up to 3 mos. later on. These records are the only in vivo derived observations on individual animals. There is no other information on such parameters, i.e., condition of fur, shivering, grooming, activity, skin color, etc., usually part of "clinical observations." High number of autolysed rats, is suggestive of infrequent observations, i.e., less than daily. There is no proof that the

			(proper) medicated feed was consumed every day by all animals on test throughout study. Rats deprived of water will not eat. No evidence as to availability of water. May have influenced large weight fluctuations. (Poor animal husbandry practices).
Ophthalmology examinations	Protocol provided for "day 7, 3 months, 6 months, 9 months, 18 months" "At termination carry out slit lamp examinations of 5 males and 5 females per group. IBT report is silent on ophthalmology. IBT admitted at inspection that no slit lamp exams were done and consulting ophthalmologist not involved who usually does them.	Syntex admits no slit lamp exams were done. Availability of selected optic nerve and eye exams are a substitute. Caretakers on weighing observed eyes.	There is no record of any observations in only document of this study relating to ophthalmology in the intact animal. Histological tissue processing, sampling, & trimming, can obscure in vivo findings, i.e., granular deposits of drug. FDA depended at NDA approval on eye exams in animals as drug had not been administered to man over extended period of time and for which pre & post eye exams were available. Observations of cataracts are often not seen on histological examination. Only 1 female of high dose survived for total 22 mos. of study. Caretakers may not be adequately trained to make and record this type of observation.

The Appendix II (Plank Report) contains data not supported by other records.

Appendix II is an integral part of the IBT report listing for each individual animal notations as to sex, dose level, approximate time of death, histological observations made by Dr. Richter who examined a long list of tissues (when available to him), histological examinations on selected tissues by Dr. Gordon in selected animals and certain gross findings.

Appendix II is used as if it were fact.

Observations of autopsy finding from some animals made on cage cards by caretakers and then transcribed to Appendix II.

Histological examinations on autolysed animals is possible. See IBT study.

Syntex claimed existence of study notebooks.

Information in necropsy log was faithfully transcribed from autopsy sheets and terminal sacrifices. The source of additional gross findings is unsubstantial in appendix II.

Dates of death in Appendix II for several animals is later than that recorded in necropsy log.

Dr. Richter only indicated tissues be found abnormal. There is no indication what he actually observed. List of tissues by Syntex suggest some tissues were not presented to Richter.

Appendix II lists gross findings not supported by necropsy log on TBA/TDA and TBA/NTT group. It fails to indicate autolysis though noted in Richter report.

Cage cards do not exist in 1976-7.

Peponderance of lung related gross pathology is reported in Appendix II; possibly added after histological data was available.

IBT report makes no reference to extant of autolysis present (58% of animals dying before 22 mos.) No mention of notebooks elicited at IBT inspection.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

MAR 11 1977

Honorable Edward M. Kennedy
United States Senate
Washington, D.C. 20510

Dear Senator Kennedy:

At yesterday's hearing on our bioresearch monitoring program before your subcommittee, you invited us to request the assistance of the subcommittee in obtaining access to a complete list of the studies performed by Industrial Bio-Test Laboratories on products approved or regulated by FDA and other Federal agencies. Specifically, you indicated a willingness to consider the issuance of a Congressional subpoena for that material. We promised to provide the subcommittee a response by the end of the day.

Our attempts to call you, Dr. Horowitz, or Mr. Fox yesterday evening were unsuccessful, but I was able to reach Mr. Fox this morning. As I have advised him, we believe that, as a result of your statements yesterday, a final attempt to obtain the information from IBT voluntarily may be successful. Last night the attached letter was sent as a telegram to Dr. Calandra, President of IBT, reiterating our insistence that the information be provided immediately or we would resort to the use of compulsory process.

We have in addition been in communication with the office of the United States Attorney in Chicago, which has expressed a willingness to consider the use of a grand jury's compulsory process to obtain the information if it is not provided voluntarily. If we do not receive a satisfactory response from IBT, we intend promptly to recommend a grand jury inquiry into the conduct and reporting of testing by that firm. One of the immediate purposes of such an inquiry would be to elicit, by subpoena, the information that is needed to facilitate our assessment of the continued approvability of products marketed on the basis of IBT-conducted tests. This approach would have the additional advantage of acquainting the United States Attorney's office with the findings and progress of our IBT investigation as it proceeds, which would shorten the time required to prepare and present any criminal enforcement action that might grow out of the investigation.

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Page 2 - Honorable Edward M. Kennedy

We will know within a matter of days whether one or the other of these approaches is likely to produce the information we need. We are hopeful that the disclosures at yesterday's hearing may provide the stimulus for IBT to provide the information voluntarily. However, if both approaches fail, or seem likely to leave the matter unresolved for any length of time, we will promptly return to the subcommittee and formally request whatever assistance, including the issuance of a subpoena, that you can provide.

Sincerely yours,

Sherwin Gardner

Sherwin Gardner
Acting Commissioner of Food and Drugs

Enclosure

cc: Honorable Richard S. Schweiker

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

March 11, 1977

Dr. Joseph C. Calandra
Industrial Bio-Test Laboratories
1810 Frontage Road
Northbrook, Illinois 60062

Dear Dr. Calandra:

On November 12, 1976, you and your associates and counsel attended an informal conference with staff of this Agency chaired by Dr. Carl M. Leventhal, Deputy Director of the Bureau of Drugs. The subject of the conference was the deficiencies found by the Bureau of Drugs in certain animal studies conducted by your laboratories. At that time, to assist FDA in expediting the identification and evaluation of all products whose regulatory status may be dependent upon studies conducted by IBT, Dr. Leventhal requested that you provide the Agency with a list of all studies conducted in your laboratories. Counsel for IBT, Mr. Merrill Thompson, acknowledged this request in his letter of November 19, 1976, to Ms. Anne Davidson of the General Counsel's office, and advised FDA of IBT's plan to provide these data.

The process identified by Mr. Thompson has proven to be unsatisfactory. Between January 11, 1977 and February 22, 1977, we have received 7 communications from Mr. Thompson providing us with the names of studies on drugs only which IBT has conducted for some 15 regulated firms. We still have no idea as to what fraction of the studies IBT actually has conducted those reported represent. We moreover, have no idea as to how many products including those under the regulatory jurisdiction of other FDA bureaus or other regulatory and scientific agencies may be affected.

As you may know, we testified on this date before the Senate Subcommittee on Health and Scientific Research of the Committee on Human Resources and the Subcommittee on Administrative Practices and Procedures of the Committee on Judiciary. Senator Edward M. Kennedy, Subcommittee Chairman, expressed his dismay at the slowness and inadequacy of your response and the consequent delay in our identification and evaluation of all studies conducted by your laboratories and their possible impact on the safety of products being consumed by the American public. We share his concern and impatience with your lack of full and responsive cooperation with our request of four months ago.

I would like to offer you final opportunity to comply voluntarily with our request that you provide a complete and accurate list of all studies conducted by your firm. We ask that you provide us within one week a

list which clearly identifies the sponsors, products, dates, and types (e.g. chronic, subacute, carcinogenicity, etc.) of all studies conducted by IBT since January 1, 1967. I would expect that you would also be prepared to provide, if requested later, a similar list of older studies conducted since the inception of your firm's activities.

I await a more responsive and forthcoming reply than we have received to date. I am prepared to utilize every legally available recourse to obtain this information as soon as possible in the absence of your voluntary cooperation. Please acknowledge receipt of this telegram within 24 hours indicating your intention to the above request.

If the information that I am requesting is voluntarily made available to FDA, the Agency will not disclose it to the public and will deny any request made under Freedom of Information Act on the ground that the information is confidential commercial information and part of an open investigatory file.

Sincerely yours,

Sherwin Garner

/s/Sherwin Garner
Acting Commissioner of Food and Drugs

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

MAR 17 1977

Honorable Edward M. Kennedy
United States Senate
Washington, D. C. 20510

Dear Senator Kennedy:

This letter supplements my letter to you of March 11, 1977. I am enclosing copies of the telegram we received from Dr. Calandra, President of Industrial Bio-Test (IBT), and the letter I sent Dr. Calandra in reply.

As my letter of March 15, 1977 to Dr. Calandra states, we are accepting the plan he proposes as an expeditious means, under present circumstances, of obtaining the information we need to assess the continued marketability of compounds tested by IBT. I believe, and think that you would agree, that this arrangement, while not ideal, nevertheless will produce the information the Food and Drug Administration needs to identify quickly the products regulated by the Agency on the basis of IBT tests. Should any of IBT's clients decline to permit IBT to identify the compounds tested, I believe that information will be readily obtainable from the firms in question.

I shall keep you informed of further developments in this matter and thank the Subcommittee again for your offer of assistance.

Sincerely yours,

Sherwin Gardner
Acting Commissioner of Food and Drugs

Enclosures

PHS PKLN ROVE

BIO TEST NBRK
MARCH 14 1977
DR SHERWIN GARDNER
FOOD AND DRUG ADMINISTRATION
EPARTMENT OF HEALTH EDUCATION AND WELFARE
WSHINGTON D C

DEAR COMMISSIONER GARDNER:

HIS LETTER RESPONDS TO YOURS DATED MARCH 11 1977. WE WERE SRPRISED TO LEARN OF YOUR DISSATISFACTION WITH THE PROCESS WHICH WE HAVE BEEN FOLLOWING TO DISCLOSE STUDY LISTS TO YOUR AGENCY. WE UNDERSTOOD THAT WE WERE COOPERATING IN A MATERIAL WAY AND AT AN ACCEPTABLE LEVEL WITH THE RESULT THAT, TO DATE, WE HAVE GIVEN YOU LISTS COMPRISED OF WELL OVER 200 STUDIES.

N ANY EVENT, WE ARE WILLING TO COOPERATE EVEN FURTHER BY IMMEDIATELY INITIATING THE FOLLOWING PROCEDURE:

BY MARCH 19TH,

1. WE WILL ASSEMBLE A LIST OF ALL OF OUR CLIENTS FOR WHOM WE HAVE CONDUCTED STUDIES BEARING REPORT DATES SUBSEQUENT TO JANUARY 1, 1967.

2. WE WILL MAIL THE ATTACHED MAILGRAM TO EACH CLIENT ON THAT LIST.

3. WE WILL HAVE PREPARED A SECOND LIST OF THE SAME CLIENTS ACCOMPANIED BY A LIST OF ALL IBT POST JANUARY 1, 1967 STUDY NUMBERS, STUDY TYPES AND REPORT DATES (BUT NOT TEST MATERIAL IDENTIFICATIONS) FOR EACH CLIENT. IF YOU WISH, YOU COULD PICK UP THIS LIST AS SOON AS IT IS READY.

BY MARCH 26TH:

4. WE WILL KNOW WHICH OF IBT'S CLIENTS HAVE DECLINED TO CONSENT TO OUR INFORMING YOU OF TEST MATERIAL IDENTIFICATIONS.

BY APRIL 1ST:

5. WE WILL PROVIDE YOU WITH TEST MATERIAL IDENTIFICATIONS TO THE EXTENT AUTHORIZED BY OUR CLIENTS, AND A LIST OF THOSE CLIENTS WHO DECLINED TO GIVE SUCH AUTHORIZATIONS.

BELIEVE THIS RESPONSE IS FULLY REFLECTIVE OF YOUR AGENCY'S INTERESTS AND OF THE PUBLIC INTEREST. WE TRUST YOU WILL AGREE. IT HAS NEVER BEEN IBT'S INTENT TO OBSTRUCT THE PERFORMANCE OF YOUR DUTIES TO THE PUBLIC.

WE WILL BE RELYING HEAVILY UPON THE ASSURANCES STATED IN THE LAST PARAGRAPH OF YOUR LETTER ACKNOWLEDGING THE CONFIDENTIAL STATUS OF THE CLIENT LISTS AND OTHER COMMERCIAL INFORMATION WHICH WE WILL BE SUPPLYING TO YOU.

MR MERRILL HAS INDICATED TO OUR COUNSEL THAT WE CAN EXPECT TO RECEIVE YOUR APPROVAL OR COMMENTS PROMPTLY. IN THE MEANTIME WE WILL BE PROCEEDING AS OUTLINED IN THIS LETTER. PLEASE FORWARD A COPY OF THIS TELEX TO MR MERRILL.

SINCERELY,

J. C. CALANDRA

DRAFT MAILGRAM

AS YOU MAY KNOW, INDUSTRIAL BIO-TEST WAS REQUESTED BY THE COMMISSIONER OF FOOD AND DRUGS ON MARCH 11, 1977, TO PROVIDE THE FOOD AND DRUG ADMINISTRATION WITH A LIST OF ALL STUDIES WE HAVE CONDUCTED FOR OUR CLIENTS. THE REQUEST IS A RESULT OF A MARCH 10 SENATE SUBCOMMITTEE HEARING DURING WHICH SENATOR EDWARD M. KENNEDY OFFERED CONGRESSIONAL SUBPOENA POWER TO COMPEL THE PRODUCTION OF SUCH A LIST IF BIO-TEST DID NOT SUPPLY IT VOLUNTARILY.

THE PURPOSE OF THIS LETTER IS TO ADVISE YOU THAT WE HAVE PROVIDED THE FDA WITH A LIST OF ALL STUDIES WE HAVE CONDUCTED WHICH BEAR A DATE AFTER JANUARY 1, 1967; INCLUDING THE NAME OF THE CLIENT, THE DATE OF THE STUDY, AND THE TYPE OF STUDY (E.G. CHRONIC TOXICITY, CARCINOGENICITY, ETC.). WE HAVE NOT PROVIDED FDA WITH AN IDENTIFICATION OF THE MATERIAL TESTED IN EACH STUDY DONE FOR YOU, BUT WE INTEND TO DO SO ON MARCH 25, 1977, UNLESS YOU HAVE INFORMED US IN WRITING PRIOR TO THAT DATE THAT YOU DO NOT CONSENT TO OUR DISCLOSURE OF THE IDENTITY OF MATERIALS WHICH WE HAVE TESTED FOR YOU. IF YOU SHOULD DECIDE THAT YOU CANNOT CONSENT, WE ARE UNDER AN OBLIGATION TO SO INFORM THE COMMISSIONER.

THE FDA HAS AGREED THAT IT WILL NOT DISCLOSE THIS LIST TO THE PUBLIC AND WILL DENY ANY REQUEST MADE PURSUANT TO THE FREEDOM OF INFORMATION ACT ON THE GROUNDS THAT THE INFORMATION IS CONFIDENTIAL COMMERCIAL INFORMATION AND A PART OF AN OPEN INVESTIGATORY FILE.

WE ARE SORRY THAT WE ARE COMPELLED TO WRITE TO YOU UNDER THESE CIRCUMSTANCES AND HOPE THAT YOU WILL UNDERSTAND OUR POSITION.

PHS PKLN ROVE
V

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

March 15, 1977

Joseph C. Calandra, M.D.
President
Industrial Bio-Test Laboratories
1810 Frontage Road
Northbrook, Illinois 60062

Dear Dr. Calandra:

Thank you for your prompt response to our telegram of March 11, 1977.

Although we do not consider the manner of proceeding you have outlined in your March 14 telex as fully responsive to our request for records, we are prepared to accept your proposal as an expeditious means of now obtaining the information we need to make an assessment of the continued marketability of compounds tested by IBT. Our acquiescence in the procedure you suggest should not be regarded as agreement by FDA that such a response to any similar future request will be regarded as acceptable.

We will arrange to have the list referred to in item 3 of your telex picked up by a representative from our Chicago District Office as soon as you advise us of its availability, and in any event no later than March 19, 1977. We will expect to receive the identification of test materials and the list of clients who decline to authorize such identification no later than April 1, 1977.

Sincerely yours,

Sherwin Gardner
Acting Commissioner
of Food and Drugs

MEMORANDUM

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

TO : Director, Scientific Investigations Staff
HFD-108

DATE: MAY 24 1976

FROM : M. Adrian Gross, D.V.M., HFD-108

SUBJECT: Overview and Suggested ~~Follow-up~~ - Inspection at Industrial Biotest Labs., Inc. Northbrook, Illinois - 4/11-16/76

Enclosed here are the EIR as well as a follow-up memorandum dated 4/27/76 from Investigator Stelter of the Waukegan Resident Post, Chicago District Office.

There are two main problems here:

A. Newport Pharmaceuticals' Isoprinosine

The cover-sheet of the EIR contains a summary of approximately a dozen deficiencies found in a long-term rat study conducted by the firm for Newport. A number of these (dirty rat cages, non-identification of diet container lids, unaccounted changes in records, incomplete information on test-agent lots, lack of analysis of the diet mixtures, lack of individual identification of the test animals, etc.) can be viewed as being largely the result of poor practices. Others, such as a high mortality amongst animals during bleeding (which was reported as if it were some kind of "natural" mortality) as well as an inadequate statistical analysis of the results can be attributed to a lack of competence on the part of the professionals associated with the study.

More serious was the absence of any records of ante-mortem observations. We were told that details of such observations were recorded on the cage cards of the animals (which would be an unacceptable practice, if true) but we were also told no such cage cards could be found by the firm despite what they referred to as a thorough search for these.

The most unsettling finding, however, was that only a relatively small part of the tumors noted grossly at the post-mortem examination of the experimental animals were submitted for microscopic examination by the consulting pathologist. Since the results of the examinations by this pathologist were the only ones reported to the client (Newport) and since the latter submitted the Industrial Bio-test report to its NDA (17-677), we have here a situation where the number of animals with tumors was grossly under-reported to the FDA. In addition to this, and quite distinct from it, the demoninators of the ratios (numbers of animals with tumor/number of animals examined) were incorrectly inflated which contributed further to an improper reduction of such rates of tumor induction. This matter is quite separate from the fact that the actual statistical methodology used in analyzing these erroneous results was also improper, as mentioned previously.

I would recommend:

a) that these problems should be brought to the attention of the NDE divisions concerned with this product (HFD-120 and 140) with a view of determining the suitability of this particular study on Isoprinosine,

b) that additional similar detailed inspections of other long-term studies conducted by the firm on other prescription drugs be carried out to determine to what extent these findings are typical of their operations,

c) that the Bureau of Foods which has, to my understanding, several contracts with Industrial Bio-Test (some of which may have been recently cancelled) be also apprised of these findings.

B. Monsanto's TCC

Both Industrial Bio-test and their client, Monsanto, refused to allow the inspectors access to the laboratory records of a two-year rat study in connection with this product.

This matter was referred by SIS to the Associate Director for Compliance (Kelsey and Gross memos of 4/20/76, appended here) and the reply (Hamilton 5/5/76 and Sage 4/30/76) is also attached.

We have prepared a draft of a letter to be sent to Monsanto for the Bureau Director's signature and this is self-explanatory. We recommend that such a letter be issued.

M. Adrian Gross

MEMORANDUM OF TELECON

BETWEEN

DR. M. L. KEPLINGER, MANAGER OF TOXICOLOGY
INDUSTRIAL BIO TEST LABS.,
NORTHBROOK, ILLINOIS

AND

ARLYN H. BAUMGARTEN, SUPERVISORY INVESTIGATOR
WAUKEGAN RESIDENT POST - CHICAGO DISTRICT
U.S. FOOD & DRUG ADMINISTRATION

SUBJECT: REQUEST FOR MONSANTO TCC STUDY
[illegible] RAT TOXICITY STUDY

DATE: JULY 19, 1976

The subject study was requested during inspections of 4-12-76 et al and 6-21-76 et al. It was also discussed with the firm during our conference of July 9, 1976. During the July 9, 1976 conference, we informed the firm that we would let them know if we actually wanted the study copied. On the morning of 7-19-76, I received a request from Dr. Allen B. Lisook of HFD-103 that his office now wished a copy of it, (See my memorandum of telecon of that date).

At approximately 1:40 P.M., I called Industrial Bio Test Labs and spoke with Dr. Keplinger. I informed him that we now wished a copy of the study and requested that the firm begin assembling it. I requested that he inform us when the copy was complete and I would have an Investigator stop by the firm and pick it up.

At the time of my telecon with Dr. Keplinger on 7-19-76, the firm's President, Dr. Calandra was away from the office. On the morning of 7-20-76, at my request, Investigator Stelter called Dr. Calandra and confirmed my request of the previous day to Dr. Keplinger.

Arlyn H. Baumgarten,
Supervisory Investigator
Waukegan Resident Post CHI-DO

AHB:mjd

Orig: CHI-DO files
cc: William R. Clark
cc: HFD-103, Attn: Dr. Gross
cc: George A. Masters
cc: Jim Kadow
cc: HFD-1, Attn: Don Ottes
cc: Waukegan Resident Post
cc: Rockford Resident Post

Dictated: 7-20-76
Typed & Mailed: 7-21-76

MEMORANDUM

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

TO : M. Adrian Gross, D.V.M., Ph. D
Veterinary Medical Officer
Scientific Investigations Staff HFD-108

DATE: October 18, 1976

FROM : Ronald H. Britten HFD-108

SUBJECT: Industrial Bio-Test Laboratories, Inc. chronic rat study (no. 9575) on TCC for Monsanto.

In reviewing the IBT chronic rat study on TCC, I have noted a number of discrepancies which, if not explainable by Monsanto or IBT, could cast doubt upon the accuracy and credibility of the study. This memo confirms and expounds upon my earlier verbal communications.

A major discrepancy was the failure of the interim report (1 year) and the final report (2 years) to correspond in the data obtained in the first year of the study. The most noteworthy area of non-correspondence was in the number of animals reported to have been on the study. The interim report stated that the study had included 480 individually housed rats. The final report stated that the study had included 280 individually housed rats, 200 rats which were housed 5 to a cage, and an additional (unspecified) number of rats which were group housed (see Attachment A). The unknown size of the experiment and an esoteric numbering system have prevented a thorough evaluation of the study.

A second significant area of non-correspondence of data was in the mortality tables. See Attachment B. The values given in each table for the first year of the study are almost completely different. I compiled my own mortality table for the T3 group to determine which of the submitted tables was correct; however, I found that neither of the submitted tables agreed with the pathology sheets.

Other tables also contained significant disparities between the data reported at one year and the data reported at the end of the experiment. For example, 53 of the 120 values on page one of the table "Summary of Mean Values, Body Weight Gain Data" were dissimilar. Many of these values were listed as "NA", or not available, in the final table although the interim table listed specific figures in every case. See Attachment C, in which I have circled the final values which differ from the interim ones.

The table "Summary of Mean Values, Urine Analyses Data, Microscopic Elements" had 7 of 40 values dissimilar between the interim and final tables (Attachment D). The Albumin table varied for 5 of 32 values (Attachment E). Additional tables were found to contain a small number of variant values: Hematocrit, Serum Alkaline Phosphatase Activity, Leukocyte Count, Erythrocyte Count, Eosinophil Count, and Lymphocyte Count (Attachments F through J).

Problems other than the non-correspondence of the interim and final reports were observed. The raw data failed to confirm that all surviving rats had received ophthalmoscopic examinations at the end of the study. The raw data for this July 1971 to July 1973 study revealed that 40 T3 rats had been examined on April 23, 1972, 20 T3 rats on August 11, 1972, and 20 control and 20 T3 rats on November 12, 1972. See Attachment K.

The raw data for control animals included a pathology log from another study, IBT 9555, Much of the data in this log had been covered during xeroxing for FDA (see Attachment M). The remaining data was represented as being from animals which had served as controls for study 9575. Additional control animals were noted in the pathology log labeled "9575". We do not know whether the "9555" study was run concurrently or even in the same room with the "9575" study. If they were not, then these animals could not be considered to be adequate controls for study 9575.

Study 9575 had four major groups of animals included in the experimental design: controls, and treatment levels 1 through 3; however, the study 9575 pathology log and a pathology sheet listed control animal no. 5 as "TC": treated control. Treated controls were not part of the reported study design; moreover, the portion of the study 9555 pathology log attributed by IBT to study 9575 included two "TC" animals: nos. 23 and 27. See Attachment M.

The actual length of the supposedly 24 month study could not be determined from the records; for example, records showed that post mortem examinations had been performed on rats GC 33, GC 51, and GC 72 during the 28th month. See the pathology records in Attachment N.

Monsanto and IBT should be asked to explain each of the apparent deficiencies noted above.

Ronald H. Britten

Ronald H. Britten

October 26, 1976

MEMORANDUM OF CONFERENCE

PRESENT:

Dr. M. Keplinger) Dr. F. Kinoshita)	Industrial Biotest Laboratories, Northbrook, Illinois
Mr. M. Thompson)	Legal Counsel to Industrial Biotest Laboratories
Dr. D. Roman) Dr. P. Wright)	Monsanto Co., St. Louis, Mo.
Mr. J. Davitt) Ms. M. K. Bruch) Dr. G. W. James)	FDA, HFD-140
Dr. M. A. Gross) Mr. R. Britten)	FDA, HFD-108
Mr. M. Kennedy)	FDA, HFD-510

SUBJECT: Trichlorcarbanilide (TCC) - Chronic study in rats (IBT #9575) conducted by IBT Labs under contract with Monsanto.

BACKGROUND:

In reviewing chronic rat study #9575, it was noticed that there were some serious inconsistencies between the interim reports and the final report written at the completion of the study. Additional questions arose upon review of the raw data. Some of the obvious discrepancies are summarized in Mr. Britten's memo to Dr. Gross dated Oct. 18, 1976 (See attachments). It was concluded that these discrepancies, left unexplained, cast doubt upon the validity of the study, and it was decided that through a meeting with IBT personnel actually involved in conducting the study, we might obtain explanation or clarification of the important discrepancies.

Dr. Roman was contacted by phone and notified of the need for such a meeting. Dr. Roman was advised that IBT personnel with actual "hands on" knowledge of the study (a Mr. Plank and a Mr. Kennedy were mentioned) would probably be best able to supply the needed information (more explicit details on the actual conduct of the study.) As it turned out, Dr. M. Keplinger and Dr. F. Kinoshita were the only people on hand to represent IBT at the meeting.

The meeting was called to order by Mr. Davitt (HFD-140) and the representatives of Monsanto and IBT were then informed by him of the difficulties Mr. Britten was having attempting to correlate the raw data and the finished reports, the interim (6 months and 1 year) and the final 2 year report.

Mr. Davitt offered the IBT representatives the opportunity to explain the design of the study under discussion and the 1 and 2-year reports. Dr. Keplinger appeared unwilling or unable to do this. At this point Mr. Britten reviewed in detail the discrepancies he had noted in the data.

Dr. Keplinger, with the support of Dr. Kinoshita, explained that the 1-year interim study was hurriedly prepared, whereas the final (2-year) report was more carefully put together and can be considered accurate. He also explained that additional animals were added to the study when it was 3 months along "in case they were needed" to satisfy FDA or NCI criteria for a carcinogenicity study. He said that a revision of the current animal disposition sheet might help in clearing up some of the confusion Mr. Britten had noted between the raw data and the final report.

Dr. Keplinger and Dr. Kinoshita were responsive to our questions on a broad general basis, but were apparently unable to speak definitively with regard to specific details in many cases.

Dr. Gross remarked that without the people who actively participated in the study, only conjectures could be made. It was agreed by the other FDA representatives present that an adequate discussion of this study and clarification of the issues at hand could only have been accomplished with the participation of these individuals. (Dr. James and Mr. Davitt reminded Dr. Roman that this had been discussed in two pre-meeting telephone conversations with him.)

It was then concluded by the FDA representatives that the study is unacceptable because the data in its present form does not permit evaluation.

Finally, the visitors indicated that they would attempt to supply additional raw data, if any existed (i.e., any data not already at Mr. Britten's disposal), together with a clear description of the study design, and that they would clarify the animal numbering system. They agreed to accomplish this by November 12, 1976.

The meeting then was ended.

George W. James, Ph.D. 11/17/76

cc:
DMF #215
HFD-140/MLGibson
HFD-140/CSO
HFD-510/Pinco
HFD-102/D'Aguanno
HFD-108/Kelsey
HFD-140/JMDavitt
HFD-140/MKBruch
HFD-108/MAGross
HFD-108/RBritten
HFD-510/MKennedy
HFD-140/GWJames:mef/11/10/76 & 11/17/76
RD initialed by JMDavitt 11/17/76

MEMORANDUM

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

TO: M. Adrian Gross, D.V.M.,Ph.D.
Veterinary Medical Officer
Scientific Investigations Staff
HFD-108

DATE: JAN 27 1977

FROM: Ronald H. Britten HFD -108

SUBJECT: Industrial Bio-test Laboratories, Inc. chronic rat study (no. 9575) on TCC for Monsanto.

In my October 18, 1976 memorandum to you, I outlined certain deficiencies which I had found in the Industrial Bio-test Laboratories, Inc. chronic rat study (no. 9575) on TCC for Monsanto. IBT and Monsanto were asked to explain these deficiencies in a meeting with SIS and the Division of Anti-Infective Drug Products (DAIDP) on October 26, 1976, but they provided little explanation at that time. In a meeting on December 14, 1976 IBT and Monsanto presented DAIDP and SIS with a written explanation of the deficiencies.

The December 14 submission (dated December 12) by IBT regarding the TCC study provided the first comprehensive description of the structure of that study and its relation to certain other studies. There were reportedly five related studies and sub-studies: the TCC primary study, the TCC sub-study, the CP primary study, the CP sub-study, and the TCC research study. We were told that the research study was run from November 1971 to November 1973, but that the other studies were run from July 1971 to July 1973.

The sub-studies were the result of placing part of the animals in individual cages in one room and the rest of the animals in group cages in another room. Although the one year interim report for the TCC study had stated that all of the 480 rats on that study had been placed in individual cages, the two year final report and the December 14 submission indicated that only 120 rats had been individually caged, the other animals having been placed in group cages.

Until the spring of 1973 the individually caged rats were kept in a different room than the group caged rats. In spring the individually caged and the group caged rats were brought together in one room at a new location.

A two year chronic rat study (IBT no. 9555) performed on another Monsanto product, which was designated CP 41845, was run at the same time as the TCC study, was also divided into individual and group caged sections, and was located in the same rooms as the TCC study. The control rats for the TCC and the CP 41845 study were shared and were, of course, also divided into individually and group caged animals. According to Monsanto, CP 41845 does not come under FDA jurisdiction.

A TCC research study consisting of 250 group caged rats was reportedly run by IBT at its own expense as a speculative venture. The controls in this study were not designed to be shared with the TCC study done for Monsanto.

The complicated pattern of experimentation described above may not be a complete description of the conduct of these studies. for the pathology sheet for TCC study rat number 44, a group caged treatment group 1 female, has the disturbing note "Started 8-1-72". None of the groups known to us was started on that date. Pathology records indicated that certain animals were treated controls. None of the studies were said to have included a group of treated controls and the use of treated controls was denied by IBT at the December 14 meeting.

The structure described above was not static for the TCC study done for Monsanto or for the CP 41845 study. Rats which died in individual cages were said to have been replaced by rats from group cages. The substitute rats inherited the indentification numbers (cage numbers) of the dead rats. The group caged TCC rats had no individual identities prior to the substitutions. No records were kept of the dates of the substitutions or the cages from which the substitute animals were taken. No ante-mortem records were retained for any animal. That the animals used for substitution were from the same treatment group or even the same study could not be verified from the IBT records; furthermore, IBT was unable to explain the numbering system for the TCC group caged animals (page 6 of the December 14 submission): "To date it has been impossible to determine from the records whether the number identification of group-housed animals were in accordance with a system or whether random numbers were used."

IBT suggested at the December 14 meeting that the month of the substitution of group caged for individually caged rats could be determined by examination of weight records; they provided a three page document listing some of the substitutions. I found this method of identifying substitutions to be inadequate. Weight records, which were kept only on individually caged rats, were generally made at intervals of one month. Some months were missed, or are missing from the records. The only way to detect substitutions would be to find instances where rats were dead one month, but present for a subsequent weighing. This method would not detect rats which died and were replaced between two consecutive weighings.

Data verification is further complicated by the absence of most or all records for some rats. According to the December 14 submission (page 8), 50 individually caged animals were represented only by weight records and 50 group caged animals were represented by no records at all.

During the October 26 meeting with IBT, I asked for an explanation of the presence in the gross pathology records of post-mortem examinations of TCC regular (non-research) study no. 9575 rats whose dates of death were several months later than the final sacrifice. The response, given at the December 14 meeting, was that all rats examined after the final sacrifice were from the research study. According to IBT, all research rats were thrown out if they died before the regular study final sacrifice, but were given gross pathological examinations if they died after that study was terminated. Post-mortem and final sacrifice examinations of research rats were, however, recorded as being part of study no.9575. The research animals were divided into treatment groups equivalent to those of the regular TCC animals.According to page 20 of the December 14 submission, "The group-housed rats in the research study were identified in the same manner as were the group-housed rats in the main study."

Acceptance of the explanation that all research animals were thrown out and that no pathological examinations were done on research animals prior to the termination of the regular TCC study would create a new problem with the data. If research and regular TCC animals were never confused by IBT in the gross pathology log, then for any treatment group the addition of the number of research animals listed as having received post-mortem examinations (rats dying after the regular TCC final sacrifice) to the number of research rats present at the research final sacrifice should be a sum less than the number of rats in that research study group. This is due to approximately half of the research rats failing to survive to the final sacrifice and some being thrown out prior to the end of the regular TCC study. I determined that there were 41 control group males and 43 control group females recorded in the TCC pathology logs as having died after the date of the TCC final sacrifice. Since the research study control group contained only 35 males and 35 females, it is evident that there is confusion as to the identity of research and non-research animals.

These figures (41 and 43) were derived from data in the CP and TCC gross pathology logs as follows:

	Male	Female
CP log post-mortem examinations subsequent to 6-29-73 final sacrifice of CP/TCC controls	10	5
CP log 11-21-73 final sacrifice of research animals	7	17
TCC log post-mortem examinations subsequent to 6-29-73 final sacrifice of CP/TCC controls	7	5
TCC log final sacrifice of research animals	17	16
Totals	41	43

The pathology logs which I used for the above determinations were supplied by IBT on 9-14-76 in response to our requests for all of the TCC raw data. We had objected at the October 26 meeting that all data for treatment groups other than the control had been blocked out when the log was copied for FDA. As part of its December 14 submission IBT supplied a copy of the log with none of the CP data blocked out. This copy, however, deleted all pages referring to the sacrifice of the CP/TCC controls. The confusion between the research and non-research animals would not have been detected in the December 14 submission.

As noted in my October 18 memorandum, many of the mean body weights in the two year report differed from those in the one year report. Some were numerically inconsistent; others were replaced in the two year report by "NA" (not available). At the December 14 meeting IBT explained that NA was used wherever the original raw data was missing. No "NAs" appeared in the one year report. Examination of the raw data revealed that particular pages had been prepared for the sets of weights, but the weights had never been entered. If one examines the values in the one year report which were replaced by "NAs" in the two year report, one finds in many cases that the "missing values" are linear interpolations of the values which were present in the raw data. The increment used in each interpolation can be calculated by determining the difference between the mean weights on either side of a gap in raw data and dividing by one more than the number of consecutive missing values. Thus, it appears that the "NAs" may not have been used to replace missing values, but fictitious ones. Examples may be seen between weeks 6 and 10 for the T I and T III males.

One of the more significant discrepancies mentioned in my October 18 memorandum concerned the mortality tables. The one year report indicated that no deaths had occurred during the first six months, while the two year report showed 33 deaths for the first six months. In addition, the interim report listed fewer total deaths for the first 12 months (70) than did the final report (94). IBT blamed the difference between the tables on confusion with the six month sacrifice (December 14 submission, page 15) animals; however, by definition there could be no mortality in sacrificed animals and IBT's explanation does not seem plausible.

The numerous discrepancies between the tables of laboratory values in the interim and final reports were not discussed in detail at the December 14 meeting. IBT stated their willingness to do so if we so requested. Raw data covering the final ophthalmoscopic examinations was not supplied by IBT until the December 14 meeting.

IBT claims to have supplied us with all available records regarding the TCC chronic study; however, a document entitled "Animal Disposition" supplied by IBT to assist us in reviewing the study has information which I have not found in the records themselves. Some of the animals have pathology identification numbers listed on the animal disposition sheets; I have seen these numbers in no other records. The animal disposition sheets indicated that 61animals had post-mortem autolysis and received no gross pathology examinations; however, the gross pathology log listed only 29 such animals.

In general, review of the raw records of the chronic study on TCC did not verify that the study data was accurately reported. Of particular concern was the failure of the records to provide assurance that the animals on test were kept segregated as to their treatment group or even their study.

False information regarding the manner in which the study was structured and performed, false mortality data, and false laboratory data, were submitted to the government in the one year report about the time when an official OTC Panel was reviewing TCC. The false submissions on structure and mortality appear to me to have the effect of making the study and the drug look better than they are. The two year report of this 1971/1973 study was not submitted to FDA until 1976, after serious deficiencies had been found in regard to other studies performed by IBT. The study was submitted only after DAIDP insisted that it be submitted. As you are well aware, we also had serious difficulties in obtaining the raw data for the study.

Another disturbing development is that a former member of the OTC panel which reviewed TCC represented IBT at the October 26 meeting at Parklawn. (See my November 8, 1976 memorandum to John Davitt, DAIDP.)

The investigation of the TCC chronic study has thus far centered on issues of scientific integrity. I recommend that an investigation of possible fraud be considered.

Ronald H. Britten

Ronald H. Britten

MEMORANDUM

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

TO : Dr. Frances O. Kelsey, Director,
Scientific Investigations Staff,
HFD 108

DATE: February the 3rd, 1977.

FROM : M. Adrian Gross, HFD 108

SUBJECT: Questionable work carried out by Industrial BioTest Laboratories (IBT)

Attached here are copies of two memoranda written to me by Mr. Britten; they represent the essence of his review of two source documents:-

a) the IBT report of a two-year rat study carried out for ICN on Virazole

b) the written IBT submission presented to us at the meeting held here on December 14th last on TCC

I have gone over with Mr. Britten in great detail into the specific problems that he identifies. He has shown me the source of each of these specific points. I would emphasize here that on the Virazole study all he had to review at this time was the report generated by IBT since we have not seen any raw data from this study. In the TCC matter, Mr. Britten has shown me the actual raw data and other information not contained in the original IBT report and I would say that his perception of the problems and difficulties encountered here are essentially correct. In neither case, however, can his analysis be considered an exhaustive one in the sense that other problems not identified by him may not be uncovered if a review of still greater depth is undertaken. I question, however, whether this is indicated or worthwhile at this time.

I certainly endorse his overall conclusion on the Virazole study that a complete raw data audit is necessary. As to the TCC matter, Mr. Britten believes false data have been submitted to the government, and I would say that it looks to me as if he is right on this. Certainly HFD-140 would eventually have to make the final decision on the acceptability of this study. I would recommend here that compliance personnel investigate the matter of the false data to determine the advisability of building a prosecution case here.

M. A. Gross

December 7, 1977

MEMORANDUM OF MEETING

Monsanto

Dan Roman, Ph.D.

George Levinskas, Ph.D.

Gilbert J. McEwan

FDA - DAIDP

George James, Ph.D.

Jack Davitt

Mary K. Bruch

Representatives of Monsanto met with DAIDP personnel to clarify issues raised at previous meetings with IBT and FDA. They were particularly concerned about the disposition of TCC in the tenative final monograph to be issued on the OTC Antimicrobial I Report. The issues in the IBT 2-year chronic feeding study performed for Monsanto were briefly discussed. Mrs. Bruch informed Monsanto that even though no final decision concerning the study had been made by DAIDP, and would not be until another meeting with both IBT and Monsanto had been held, the

decision concerning categories for the OTC monograph could not wait. She had concluded that for these purposes, TCC could not be considered Category I. This study had formed the basis for safety factor calculation for TCC and that from her review of the problems associated with the study there is no way to extract useful data to be applied in this way. She told Monsanto that another 2-year study with a carefully developed protocol and attention to TCC absorption and possible uptake of TCC by the lymphatic system would be necessary before TCC could be placed into Category I.

The forthcoming meeting on December 14, 1977 with Monsanto and IBT was discussed and confirmed.

Mary K. Bruch

Mary K. Bruch
Executive Secretary
Microbiologist

cc:
HFA-224
HFD-140
HFD-140/James
HFD-140/Davitt
HFD-140/MKBruch

MEMORANDUM

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

TO : Richard A. Merrill
General Counsel, (GFC-1)

DATE: 27 JAN 1977

FROM : Acting Director,
Bureau of Foods, (HFF-1)

SUBJECT: FDA Contracts with Industrial Bio-Test Laboratories (IBT)

1. Your memorandum of January 7, 1977, posed the following question to the Bureau of Foods:

"What actions has FDA taken to monitor and, more recently, suspend or revise work done by IBT under contract to FDA?"

2. The Bureau of Foods has negotiated four (4) contracts with IBT:

(a) 223-74-2155 - "Determine Levels of T-2 Toxin in the Diet Which can be Considered Safe for Human Consumption" (Project Officer: Dr. T. F. X. Collins);

(b) 223-74-2177 - "Evaluation of the Toxic and Teratogenic Effects of Selected Chemical Substances During Gestation in Mammals" (Project Officer: Dr. T. F. X. Collins);

(c) 223-74-2232 - "Acute and Intermediate Duration Toxicity Test of Ipomeamarone in Rats" (Project Officer: Mr. W. I. Jones); and

(d) 223-74-2235 - "Study of Influence of Zinc on the Tissue Deposition and Chronic Toxicity of Cadmium" (Project Officer: Mr. S. Graham).

Each project officer of the above four contracts was asked to respond to the question asked.

3. Contract 223-74-2155 (T-2 Toxin)

This contract was initiated on June 28, 1974, and expired on September 30, 1976. Lack of quarterly technical progress reports was encountered early during the active period of the contract. The project officer made his first site visit on December 15, 1975, and the work appeared to be on schedule. A second site visit was made by the project officer on July 19, 1976. The contractor indicated the experiment was on schedule and FDA would receive a report by the end of August 1976. On August 24, 1976, a letter was sent to IBT stating they had failed to submit technical progress reports and that FDA was concerned that IBT should follow the Scope of Work under contract. A telephone call was made to IBT following the letter. The final report was

received in FDA dated October 15, 1976. A final site visit was made to IBT on December 1, 1976. At that time, the project officer was accompanied by Ms. Roberta Gjolstad, Contract Specialist. (Additional details are summarized in Attachment I "Site Visit Report of December 1, 1976", and in Attachment II "Project Officer Reply to Mr. Merrill's Question"). This contract is currently being closed-out by the Division of Contracts and Grants Management.

4. Contract 223-74-2177 (GRAS Review Substances)

This contract was initiated on June 24, 1974, and expired on September 30, 1976. The contract was to determine the toxic and teratogenic effects of twenty (20) selected GRAS compounds. The original expiration date for the contract was June 30, 1975; numerous telephone calls were made during this time by the project officer to IBT to obtain the teratology reports. The expiration date was extended three times until the final date of September 30, 1976. The project officer made the first site visit on December 15, 1975. At that time, he learned of the communications problem between the administrativ staff and the technical staff conducting the experimentation. On February 27, 1976, the first reports, covering the use of rats as the experimental animals, were received. The complete series of rat reports were received during the next several months. The lack of proper controls in some experiments was determined and IBT was notified. A second site visit was made on July 19, 1976, to discuss several questions raised by the project officer after studying the reports. Also, the mice reports had not yet been received at that date. On August 24, 1976, a letter was sent to IBT which reviewed deficiencies in performance of this contract. A meeting was held on October 24, 1976, with personnel from the Negotiated Contracts Branch to discuss which reports would be acceptable to FDA. The most recent site visit to IBT was made on December 1, 1976, to monitor this contract. (See Attachments I and II for additional details). At the present time, there is a continuing dialogue between FDA and IBT to resolve several differences concerning technical reports and deliverable data to FDA.

5. Contract 223-74-2232 - (Ipomeamarone)

This contract was initiated on June 28, 1974, and expired on June 27, 1976. The contract required an acute toxicity test (LD_{50}) and an intermediate duration toxicity study to include reproductive, mutagenic and teratogenic testing. During a period of approximately eighteen (18) months, IBT completed the acute toxicity testing. IBT filed their report on December 31, 1974. The Food and Drug Administration was not able to supply additional ipomeamarone to IBT to conduct the intermediate toxicity tests. The contract was terminated by mutual agreement between representatives of IBT and FDA. Currently, this contract is in the process of being closed-out by the Division of Contracts and Grants Management. For additional details, see Attachment III (Response by Project Officer to Mr. Merrill's Question).

6. Contract 223-74-2235 - (Zinc and Cadmium)

This contract was initiated on June 28, 1974, and was originally scheduled to expire on June 27, 1977. The purpose of the contract was to determine whether varying the level of zinc in the diet can protect against or increase susceptibility to the hazard of cadmium. A chronic feeding study was initiated in rats to determine the influence of zinc on tissue deposition and chronic toxicity of cadmium. At the end of October 1974, the project officer had not received the first progress report. As of the end of March 1975, none of the progress reports had been received in FDA. While making arrangements with the Principal Investigator at IBT for a site visit, the project officer learned that the chronic study had been delayed and that it did not begin until December, 1974. Also the experimentation was underway at Decatur, Illinois, rather than in their laboratories near Chicago. The project officer made an on-site visit to Decatur on June 9, 1975. IBT was reminded of the requirement to submit progress reports. However, no reports were received through February 1976. Several contacts were made with the Principal Investigator in February 1976. On March 8, 1976, the project officer returned to Decatur where he received an incomplete progress report. Upon review of the first data submitted by IBT, the project officer realized that the experiment would not last through the negotiated contract time because of the high rate of premature deaths of the experimental animals. Subsequently, it appeared that increased grooming due to diet deficiencies was the main contributing factor in the animals' deaths. The project officer returned to FDA; he called a meeting of the Project Advisory Group (PAG) and reviewed the status of the project. The PAG advised that the contract should be cancelled. The Division of Contracts and Grants Management was notified of the seriousness of the problem and they took action to begin termination of the contract. The contractor was to submit the final report by May 14, 1976. It did not arrive. On July 19, 1976, the project officer returned to IBT to request the final report and the raw data on which it was based. The final report was received in FDA on October 7, 1976. On December 1, 1976, Ms. Roberta Gjolstad, DCGM, on a site visit to IBT, again reminded them to send the raw data to FDA. As of today's date, FDA has not received the raw data promised on July 19, 1976. See Attachment IV for additional details (Project Officer Response to Mr. Merrill's Question). The Division of Contracts and Grants Management is continuing pressure upon IBT to submit the raw data mentioned above.

7. The preceding paragraphs are necessarily brief in order to summarize monitoring actions taken by FDA. If you require additional information, please contact Dr. Herbert Blumenthal (245-1247) or Dr. Robert G. Coon (245-1098)

for D. W. Roberts
Howard R. Roberts, Ph.D.

Attachment:

Monsanto

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March 10, 1977

Monsanto Company applauds the efforts of the Health Subcommittee chaired by Senator Edward M. Kennedy to investigate potential abuses in nonclinical laboratory test procedures by private, independent laboratories. If abuses are found, we hope the Subcommittee will recommend remedial action. This would clearly serve the national interest and such action is consistent with Monsanto's own interest in developing reliable data for evaluating the biological effects of chemicals.

In 1971, Monsnato contracted with Industrial Bio-Test Laboratories to conduct a two-year feeding study to determine what levels of the chemical TCC would affect target organs in rats. This study was initiated as part of Monsanto's overall commitment to ensure safety of the products it markets. The study, looking at long-term oral effects of TCC, was not done in response to any government request or because of any previously observed adverse effects. In fact, more than a dozen previous studies, including oral, eye and skin tests with animals, and patch and skin tests with humans, had been completed. On the basis of those studies, the Food and Drug Administration's Bureau of Drugs had approved TCC for use in

bar soaps as a bacteriostat.

In response to narrowly focused criticism of elements of the procedure used in the tests, Monsanto has conducted its own thorough review. Based upon this review, Monsanto believes that these objectives were attained. The objective of the 1971 test was to identify target organs and the levels of TCC which do and do not induce effects when measured against a group of control animals. A sufficient number of animals was examined to make the assessment of the results obtained and the conclusions which were drawn valid. This study, moreover, was conducted in accordance with the protocols and practices consistent with those used in most laboratories at that time.

Our review of the records and the results of the study have led us to conclude that the protocol, scientific conduct and conclusions of this particular study are valid. The 1971 test was conducted on large groups of animals. Identification of individual animals is not considered necessary to observe and document gross and microscopic pathologic effects. Identification of individual animals would not have increased the basic utility of the test data to make valid judgements about the effects of TCC.

Monsanto concludes, therefore, that criticism of study procedures does not have any substantive bearing on the conclusions drawn from this specific study. We do not believe the study conducted by Industrial Bio-Test needs to be repeated, based upon

our own analysis of the laboratory information. Should any additional tests be undertaken, we are confident that the same findings and conclusions would be reached.

Senator KENNEDY. Mr. Gardner, if you could go to the issue of saccharin.

Yesterday you announced the withdrawal of saccharin from the market.

As I understand it, this was based on animal tests which showed saccharin to be a potential carcinogen; is that correct?

Mr. GARDNER. That is correct. The Canadian Government has conducted studies of a period of 3 years. These were long-term feeding studies, which were recently completed. The results indicated that bladder tumors were significantly found in the offspring generations. That led to the finding of saccharin as a carcinogen in animals, which automatically requires our taking action to remove it from the food supply.

Senator KENNEDY. Can you tell us a little bit about what kind of products are involved in this?

Mr. GARDNER. The largest use of saccharin is in soft drinks, soda pop essentially, which constitutes about three-quarters of its use.

Senator KENNEDY. That is how much?

Mr. GARDNER. About three-quarters of the use of saccharin in this country. It is also used for sweetening canned fruits, cakes, and other such products. There is a small amount used in drugs, and a smaller amount used in cosmetics.

Senator KENNEDY. What are the substitutes that are available on the market?

Mr. GARDNER. Mr. Chairman, there are no artificial sweetners other than saccharin that are now approved for use in this country.

Senator KENNEDY. Is it unsafe, in your opinion, or the opinion of FDA?

Mr. GARDNER. Is saccharin unsafe?

Senator KENNEDY. Yes.

Mr. GARDNER. Yes, it is unsafe to the extent that animal results are projectable to human experience. That is the best judgment of scientists today.

Senator KENNEDY. You have got 80 years of use by human beings, have you not?

Mr. GARDNER. That is correct.

Senator KENNEDY. Have you any medical information that this has caused a health hazard, or cancer, in any——

Mr. GARDNER. There have been no findings relating to the use of saccharine to human illness. Perhaps Mr. Ronk, who is with the Bureau of Foods, could shed a little more light on that.

Senator KENNEDY. Mr. Ronk.

STATEMENT OF RICHARD RONK, DIRECTOR, DIVISION OF FOOD AND COLOR ADDITIVES, BUREAU OF FOODS

Mr. RONK. I believe there are no human epidemiology studies that indicate that use of artificial sweetners in diabetics leads to an increased incidence of bladder cancer. In fact, I believe there was a study done; it was published in the British Journal of Preventive and Social Medicine, November 1974, "Bladder Cancer Mortality in England and Wales in Relation to Cigarette Smoking and Saccharin Consumption" by Armstrong and Doll, which would indicate the opposite.

Senator KENNEDY. Could you give that to me again?

Mr. RONK. There is an epidemiology study that was conducted in England by Armstrong and Doll, which was published in the British Journal of Preventive and Social Medicine, November 1974, which would indicate that there is not an increased incidence of bladder cancer in relation to artificial sweetners.

Senator KENNEDY. Is that the only one?

Mr. RONK. There are two more studies, the first by Irving I. Kessler, "Cancer Mortality Among Diabetics," Journal of the National Cancer Institute, 1970, and Bruce Armstrong, A. J. Lea, A. M. Adelstein, J. W. Donovan, G. C. White, and S. Ruttle, "Cancer Mortality and Saccharin Consumption in Diabetics," British Journal of Preventive and Social Medicine, 1976.

Senator KENNEDY. You give them liberty in terms of the scientific information and the presentation, those are valid studies?

Mr. RONK. Yes.

Senator KENNEDY. That is your conclusion about it?

Mr. RONK. That is really not my conclusion; that is the conclusion of the scientists that advise me.

Senator KENNEDY. How long do you think it would take, or do you estimate it would take to go through the new process?

As I understand it, of course, there are many people that need saccharin as a medical necessity, are there not?

Mr. GARDNER. Dr. Crout can answer that.

Senator KENNEDY. They need a sugar substitute?

Dr. CROUT. Needed as a medical necessity I believe is too strong. That is one of the issues we will have to discuss here rather promptly, in the near term.

Senator KENNEDY. What about diabetics?

Dr. CROUT. I think diabetics need sugar restriction. Whether you need, as a medical necessity, some alternative that makes things sweet, is another question. It makes life more pleasant. I suspect it is not in the league of medical necessity.

Senator KENNEDY. What will be the economic impact of the removal?

Mr. GARDNER. We have not fully assessed that.

Senator KENNEDY. What do you think? Are we talking about millions, or billions?

Mr. GARDNER. We are talking about hundreds of millions of dollars.

Senator KENNEDY. It is dramatic.

Mr. GARDNER. It is dramatic.

Senator KENNEDY. Even though it is a carcinogen with regard to animals, it may not be a carcinogen with regard to human beings?

Mr. GARDNER. That is true.

Senator KENNEDY. It may be.

Mr. GARDNER. It may, also.

Senator KENNEDY. But it may not? That is what you are trying to determine.

Mr. GARDNER. That is correct.

Senator KENNEDY. Have you considered the question of labeling in terms of giving full notice to the consumer so that they have a complete label or information in terms of——

Mr. GARDNER. Labeling as it applies to foods?

Senator KENNEDY. Anything that has saccharin content, whether it is soda pop or whatever, it interests us that we have got other things.

one thing we have got no question about is smoking, and you do not ban that. We see all the implications it has in terms of overwhelming scientific information in terms of cancer, let alone the really uncontroverted testimony with regard to pulmonary disease, yet they have made a judgment that this is going to be a matter left for public information. People are going to have a warning in terms of this particular item.

I'm just wondering whether you meet responsibilities in terms of a personal notice, in terms of labeling issue or question? Have you thought about it? And if so, what is your view?

Mr. GARDNER. We have thought about it, but not really done anything with it because there is not an available option for any products marketed as foods. The law flatly prohibits the use of a substance found to cause cancer. If it is a carcinogen in animal systems that are properly tested, then there is no alternative but to prohibit use in foods—labeling aside.

Senator KENNEDY. When do you think you will find out?

Mr. GARDNER. Find out what?

Senator KENNEDY. If it is going to be a potential carcinogen, or can you find out?

Mr. GARDNER. In human beings? I do not know if we will ever find that out.

Senator KENNEDY. I do not think there should be any question but that the agency acted wisely in taking the action which they have taken.

It presents obviously an enormous dilemma in terms of adequate protection of the American people. These are some of the factors that have to be balanced.

I strongly believe that in terms of this question you have to come down, as you should, on the side of the protection of the consumer.

I suppose we have to figure out what we are protecting the American people from. That is really the nub of it, it would appear to me.

We would expect to hear from you, Mr. Gardner, just with regard to what information you think in terms of the IBT for us to request in the form of a subpena. Our interest in requesting it, quite frankly, would be in our responsibility as a legislative committee that is attempting to deal with a legislative mandate of the FDA to protect the American people in situations as you described here this morning, which I think clearly reflect that there are serious existing procedures which have to be followed by the FDA under existing law prior to the time of removal of any of the drugs, and that I think is an issue that raises very important public policy questions. And getting the facts on this particular research organization and finding out what material they do have can be extremely valuable and helpful to us in measuring the severity and importance.

It is in that spirit that we go to the members of the committee and request that we subpena that information.

The subcommittee stands in recess.

[Whereupon, at 12:03 p.m., the subcommittee was recessed subject to the call of the Chair.]

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