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Joan Claybrook, President

October 27, 1994

David Kessler, M.D., J.D.
Commissioner, Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, MD 20857

RE: CRIMINAL PROSECUTION OF THE UPJOHN COMPANY

Dear Dr. Kessler,

Six months ago, on April 25, 1994, we asked you to refer The Upjohn Company to the Justice Department for criminal prosecution because it withheld vital information from the FDA and misled the agency about the safety of its top-selling sleeping pill, Halcion. Our letter was based on an April 4, 1994 FDA memo which summarized evidence obtained during an FDA inspection of the firm from December 1991 through March 17, 1992 -- an investigation that was abruptly terminated without an adequate explanation. The Summary of Findings in this memo concluded that "the firm has engaged in an ongoing pattern of misconduct with Halcion."

We have just obtained additional FDA documents which shed new light on this investigation, raise serious questions about the propriety of the abrupt termination of the investigation and strongly suggest a high-level FDA coverup. A March 26, 1993 FDA memorandum from D.M. Erspamer (FDA field investigator) to Kenneth P. Ewing (supervisory investigator) regarding the 1991-92 FDA inspection of Upjohn included a chronology of events regarding the Upjohn investigation:

"3-17-92 [the day the investigation was abruptly terminated]: In a conference phone call with [FDA] headquarters personnel, I was told to discontinue the investigation at the firm. This directive was issued in spite of the fact that Upjohn had called to tell me that the records we had requested were ready for us to pick up, records that were deemed to be extremely important to the investigation. I specifically requested that we at least be allowed to pick up the records that we had previously requested, before discontinuing the investigation. Dave

Haggard [from the field investigations branch of the Office for Regulatory Affairs] was adamant that we should not go back into Upjohn even to pick up records that we had previously requested....A number of internal [FDA] headquarters memos were generated following the ad hoc meeting [held in Rockville, MD on May 12, 1992]. Among them are...an 11-19-92 memo of telecon between Ross Laderman [Deputy Director of Division of Scientific Investigations in FDA's Office of Compliance] and George Ishler, Corporate V.P., Upjohn....[this] memo states that Dr. Ishler related that he had been informed that Drs. Kessler and/or Peck [former Director of FDA Center for Drugs] had some informal communications with [Upjohn's] Drs. Cooper and/or Novitch [former Acting FDA Commissioner and Deputy FDA Commissioner who became Vice President of Upjohn], the resulting message of which was that FDA had concluded its investigation of the Halcion matter."

At the time of the termination, the FDA had been involved in an inspection and investigation of Upjohn for three months. The investigation was conducted to determine whether Upjohn's new drug application submissions for Halcion contained factually false information and whether the company had withheld damaging information. The FDA investigators reviewed raw data, internal Upjohn memos, correspondence and other documents, and interviewed current and former Upjohn employees. Evidence of concealment, falsification of data, and other serious wrongdoing on Upjohn's part were found, some of which were referred to in our April letter to you. However, the inspection was suddenly terminated on the eve of FDA's coming into possession of "extremely important" records. This is suspicious. What did the FDA fear was in those documents that the FDA did not want to see? Who at high levels of FDA ordered the Office of Regional Operations investigator David Haggard to terminate the investigation at Upjohn and to adamantly oppose the FDA's coming into possession of the records? FDA investigator Erspamer's March 26, 1993 memo concludes by stating, "I still have strong feelings that Upjohn has manipulated and misrepresented the Halcion data to FDA and that the firm misled the agency from start to finish."

In another memo, dated June 3, 1992 from FDA's D.M. Erspamer to George Prager/Bob Young (Office of Compliance at FDA's Center for Drug Evaluation and Research), the investigator states the following: "Although it seems clear that Upjohn's actions regarding Halcion were and are criminal in nature, it is also clear that we don't currently have sufficient evidence for a criminal case." Perhaps the "extremely important" additional documents from Upjohn could have given the agency sufficient evidence for a criminal case.

We are aware that, subsequent to our April 25, 1994 letter, you convened an internal FDA task force to investigate Upjohn's

conduct in respect to Halcion. Did this task force have the benefit of examining the records that the FDA headquarters staff was "adamant" - in 1992 - should not be picked up? If not, then the task force is working without the benefit of all information that it should consider. These records must be obtained from Upjohn, if the FDA has not already done so.

In addition to the information in these internal FDA memos, new evidence revealed during the recent trial in the United Kingdom, The Upjohn Company v. Professor Ian Oswald and the BBC, gives further substance to our fears that Upjohn engaged in a pattern of withholding information and misleading the agency concerning Halcion. Although Upjohn had concealed evidence of its misconduct in the past, using gag orders and copyright laws to suppress evidence uncovered by attorneys for damaged plaintiffs, many documents and other evidence not previously made public were disclosed during the Oswald trial, which was concluded on May 13, 1994.

Four examples, any one of which could be grounds for criminal prosecution, are taken from three different studies in which Upjohn either failed to submit data to the FDA or altered data that was submitted. See attachment for details of the following instances of data withholding or manipulation:

1. An investigator in Protocol 6047, Dr. Lahiri, enrolled 27 patients who received Halcion, yet neither he nor the patients were included in the New Drug Application (NDA) submitted by Upjohn to the FDA. In other words, this study did not exist as far as FDA was concerned.

2. Records of sixteen patients "disappeared" from Dr. Schlain's (another Protocol 6047 investigator) NDA records without explanation.

3. In Protocol 6023, there were marked discrepancies between Upjohn's technical reports and the case report forms from which the technical report was derived: of the total 22 psychiatric symptoms noted in 33 subjects, 50% were not noted in the technical report table.

4. There were wholesale omissions of drug-induced medical events such as paranoia from the Protocol 321 technical report.

CONCLUSION

We demand to know what high-level official at FDA ordered the abrupt termination of the Upjohn investigation just before the FDA was to come into possession of "extremely important" documents, and was "adamant" that the documents not be picked up by the FDA field investigator. We also urge you to carefully take note of the excerpts we included from the Oswald trial that

provide further support for our assertion that Upjohn has engaged in an ongoing pattern of misconduct and withholding information about Halcion. It is time for the FDA to criminally prosecute this firm and to remove this dangerous drug from the market in the U.S., as we petitioned FDA to do in July 1992 and as has been done in other countries such as the United Kingdom. At the very least, you must explain to us and the American people how a drug company can engage in an extensive pattern of withholding records and deceiving the FDA regarding a high-selling drug and yet avoid criminal sanctions. We look forward to a prompt response to this letter.

Sincerely,



Joanne C. Mott, J.D., M.P.H.
Staff Attorney



Sidney M. Wolfe, M.D.
Director

PUBLIC CITIZEN HEALTH RESEARCH GROUP

ATTACHMENT

All of the information presented below was derived from the transcripts of the Oswald trial (the day of trial, date, page, and line reference follow the excerpts).

PROTOCOL 6047

The Food and Drug Administration requires the sponsor of a new drug to first submit an Investigational New Drug Application (IND) in order to carry out Phase I, II and III studies, then file a New Drug Application, which must be approved by the FDA before the drug can be sold. Protocol 6047 was a 42 day double blind controlled clinical trial comparing 0.5 mg Halcion (still the upper limit of the recommended dose range) with a placebo in 125 patients with insomnia. The investigation took place largely during 1974. It was one of 10 studies regarded by the FDA as supportive of approval and was the longest supportive trial.

1. Dr. Lahiri - This doctor enrolled 27 subjects (Day 3, Page 26, line 52 to Page 27, line 11). Most of them dropped out. None of the data were reported to the FDA although Upjohn had an NDA obligation to do so (Day 20, Page 36, line 36 to Page 38, line 3). In fact, Dr. Lahiri himself was not reported as an Upjohn investigator to the FDA in the NDA although Upjohn concedes that Dr. Lahiri had given drug to patients (Day 44, Page 65, line 38 to line 56, Page 66).

Mr. C. Gray, counsel for Upjohn: And if we turn on past a number of reports about this study, and go straight to p.89, do we see a manuscript note which Mr. Sauer [employee of Upjohn] said was in his handwriting:

Talked with Dr. Lahiri at his office in the Detroit area with regard to the triazolam 6047 study... He claims that he left all the data in his Veterans...Administration office ... he was never informed of the requirement for him to retain the data for two years post NDA approval or termination of the IND. Feels he bent over backwards in helping us. Will attempt to find the list of the names of the VA patients who participated in the study and mail it to me.

Gray, (cont'd):

Is it not blindingly obvious from that contemporaneous document that what Upjohn was trying to do was to get hold of the data from Dr. Lahiri and that they were unsuccessful? Is there any other possible reason for that document?

Prof. Ian Oswald, defendant: It certainly appears that they were trying to get hold of his data. It's not absolutely

clear to me that they haven't got any. The "all" could refer to that which had been left in his VA office as opposed to made available at some other point, but what is clear is that he had patients who received drug.

Q. I do not think that is in issue. I think what is in issue and what I am asking you questions about at the moment is the allegation which I understand to be made and persisted in that there was data, that Upjohn had it and Upjohn suppressed it. Do you persist with that allegation in the light of this amongst other documents?

Prof. Oswald: Upjohn must have had data that his patients took drug and that he had some dropouts. That is data and Upjohn didn't tell the FDA in volume 1.11.

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Mr. D. Eady, counsel for BBC: As to 6047, we submit as follows:

...there was a third investigator called Lahiri. Thus the Upjohn assertion to the FDA (Statistical Report 700-5067 and Summary 700-5047 in Add.App.13) "There were two investigators" was untrue.

2. Dr. Schlain - Sixteen patients disappeared from the NDA records from Dr Schlain's [clinical investigator] arm of Protocol 6047 without explanation. In addition, seven patients were re-entered by Schlain. Upjohn was aware of this but did not communicate it to the FDA (except in the case of one patient) although Upjohn acknowledged that this was a wrongful practice (Day 20, Pages 60 to 64).

Mr. Eady's opening statement: It appears that 16 of Schlain's patients have been omitted from records and thus concealed from regulatory authorities. Startz [doctor formerly employed by Upjohn] claims that no patients numbered 1,2,3,9 or 10 ever existed. The defendants contend they did exist and must have been among the missing 16, as well as being among the first 16 patients (coincidentally the same figure) enrolled by Schlain by 22nd October 1974. Upjohn also rely on a Shipping Order for Investigational Supplies, which purports to support their case, but the Defendants claim that it cannot be accurate. There is an obvious parallel with Protocols 6045 and 6048.

As was common, Dr. Taylor did not enroll 96 patients, so as to use all the 96 bottles allocated, but only 62 numbered 1-61 and 96. The original patient No.4 dropped out and a replacement was found who took pills from bottle 96 and was therefore correspondingly numbered. Schlain purportedly enrolled 63, with a disparity in that 29 appeared to have been on triazolam and 34 on placebo. This would not have happened if he had enrolled patients in ascending serial

order 1-63 (as the Protocols all required). But there are no CRFs for 16 numbers. Of these 10 would have been on triazolam and six on placebo.

Starz seeks to explain this oddity by asserting the following propositions: Schlain was never sent bottles at all corresponding to those missing numbers (thus he received a non-sequential hotch-potch of bottles) but no good reason is given; He was sent only 81 sets of bottles (not divisible by six and therefore not an even number as between triazolam and placebo).

This flies in the face of (a) the instruction to make up bottles 1-96 and (b) the "forced" randomisation for this specific Protocol. The contention is not only inherently implausible but also is inconsistent with contemporaneous records, i.e., the CRA contact report forms completed by Upjohn's clinical research associate (CRA). From these it is clear, and the reference is given, that 14 were "on drugs" by 22nd October and two had dropped out. Yet of the first 16 disclosed to the FDA (i.e. numbers 4-8, 11-18, 24-26) five had not even been enrolled by that date, and that emerges from Dr. Adam's table 2. The only logical explanation is that the normal practice had indeed been followed of enrolling 16 patients in ascending serial order (including those now "missing"). Similarly the contact report for 11th November 1974 shows that 11 were then "on drug", a figure which can only be achieved if the missing patients 9 & 10 and 19-23 are included.

Starz also asserts that there was no patient No.23 but this too is incompatible with the contact report of 3rd January 1975 (App. 8), which shows that patient No.23 received medication (triazolam according to App.1). The tear-off label for No.23 was actually attached.

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Mr Eady: ...If it be the case and whether this is right or not, we in 1994 do not know, but if it were right that there were forty-four completed cases they would need, of course, to be all in the records and properly accounted for to the regulatory authority, would they not?

Dr. Joseph Assenzo, biostatistician, formerly employed by Upjohn: Yes.

Q. And if we are right in reading these figures, as I have read them here, and I may not be, but if I am then we add forty-four as completed to seven who are patients on drug, that takes us to fifty-one, and we add eight, that is fifty-nine. In fact, can I ask you just to look for comparison at appendix nine in the same bundle, that last page, and we have here part of the accounting to the FDA (as you will see

from the previous page) in respect of Schlain's arm and on the second page we see in the middle of the page, just under the word "confidential" ... we can see this: "In the placebo group eight patients completed the forty-two days", do you see that?

A. Yes.

Q. Fourteen patients dropped out during the course of the study because of ineffectiveness of medication. Two patients dropped out of the study because of intolerable side effects. In the triazolam group fourteen patients completed the entire forty-two days in the study, four dropped out because of ineffectiveness and one patient dropped out because of intolerable side effects."

So what we have there, do we not, is an accounting to the FDA of a total of 22 completers, fourteen on triazolam, eight on placebo, is that right?

A. These are evaluable cases? So it is 22 evaluable completers, there may have been some non-evaluables that completed.

Q. ...Now, even if we are talking about patients who are non-evaluable in the Upjohn sense, as we saw earlier they do not get lost altogether so far as the records are concerned, do they, because it is necessary to keep a record of them if they have been on drug at all?

A. Yes.

Q. And if there were 44 completed cases on 24th June it would be appropriate, would it not, to account for the difference between 44 completers and 22, giving an account of why the other completers were unevaluable?

A. Yes, but we would also have to understand what CRA's definition of completers is and what this definition of completers is.

Q. At any rate, you would agree with the general proposition -I think it is a matter of common sense - that if there were 44 completers there should be a proper record of the difference and they should be accounted for?

A. Yes.

Q. Thank you. If I can just ask you to look at appendix ten...just at the end of that you will see highlighted "Number of patients receiving each medication. Triazolam, 0.5 29, placebo, 34." Do you see that?

A. Yes.

Q. Can I ask you again about this question of people re-entering because even if it were right that in the nineteen seventies it was considered appropriate to re-enter patients more than once, it would not be right, would it, to account to the FDA in respect of them as though they were indeed, two people? Because if you have a person entering twice or three times it is still one person, is that not right?

A. I think in the - I can only tell you how I would do it. If I was doing it I would indicate that - let us say there

were twelve and two of those had been entered twice, then I would say two of the twelve were entered twice.

Q. ...Yes. It should be made known?

A. Yes.

Q. Yes, thank you. Because the number of bodies matters when you are talking about who has received drug?

A. That is correct, yes.

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Mr. Eady: But can you offer any explanation as to how it could be right if there were in a protocol seven re-entries but only one of them should be owned up to the FDA, as for example here, patient number 71.

Dr. Assenzo: I have no idea.

Q. It would not be right, would it?

A. As I told you before, if I were doing the summary I would identify that 7 patients had been entered into the study twice, but I told you before that the FDA did not prohibit doing that so I would judge right and wrong on that basis.

Q. When you say they did not prohibit it, there is nothing that you know of, is there, which sanctions it?

A. At the time, no. I didn't see anything.

PROTOCOL 6023

3. In the original NDA for Halcion, in a number of the clinical trials, there often were marked discrepancies between Upjohn's technical reports and the case report forms; this was most striking in Protocol 6023 where of the total 22 psychiatric symptoms noted in 33 subjects, 50% or 11 symptoms were not noted in the technical report table (Day 52, Page 8, lines 7-25).

Mr. G. Shaw, counsel for Prof. Oswald: That is in relation to 6023, is it not, the Sunshine study.

Dr. Anthony Kales, sleep research expert: Yes, sir.

Q. One sees "Results" at the second paragraph:

Symptoms described by van der Kroef were frequent in the triazolam group and only rarely seen in the flurazepam group.

Here did you have access to the case report forms themselves?

A. Yes, we did, and we say in the next line that the summary table does not agree with the case reports. In other words, half of the symptoms, of the van der Kroef symptoms, are not in the summary statement which is what the monitor is likely to read. A monitor that has to go through hundreds and hundreds of volumes, as Dr. Woo pointed out, as I mentioned earlier, she said: "These are very hard to find," so these

22 of the 33 patients had van der Kroef symptoms, but looking only at the summary you would only see half of that.

PROTOCOL 321

4. Protocol 321 was a Phase I tolerance study, lasting from 5/16/72 through 6/3/73. Upjohn underreported the adverse reactions associated with Halcion during Protocol 321. By not counting reports of paranoia, and by adding reports of paranoia to the placebo group that had never occurred, Upjohn changed Halcion's side-effect profile, and transformed the rate of adverse reactions into statistical insignificance. In this way, Upjohn falsified its report to the FDA on Protocol 321, in violation of Federal Drug regulations, including 21 C.F.R. 314.ff.

Day 2, pp 46-47: Opening statements by Mr. Shaw, counsel for defendant, Dr Oswald:

In Upjohn's 1973 report on Protocol 321 only four events of nervousness among men on triazolam 1 milligramme were displayed yet there were over 70. That was a statement they [Professor Oswald and colleague] felt able to make, notwithstanding Professor Oswald's role as expert in Grundberg, having been to the FDA in November. The technical report discloses only two subjects with paranoia associated with Halcion 1.0 mg. However, case report forms reveal seven subjects of the 28 with paranoia (Day 2, Page 27, line 56 to Page 28, line 5).

At p. 567, your Lordship has a table corresponding to table 5 of 1973, the same thing: "Most frequent symptoms on placebo," with italics there too, again representing omissions in 1973. On p.569, one has table C4, stated at the bottom of the page to correspond to table 6 of 1973, which was: "Miscellaneous symptoms on 1mg of Triazolam."

My Lord, that introduces five new triazolam subjects with paranoia. Subjects eight of ten were already recorded, the new subject with paranoia is subject 9, p.571. That comes for him towards the end of his entry at the top of p.572, the second line. The next new paranoia subject is subject 20, whose entries begin at the top of p.574: 'Very paranoid on day 10'. The next new paranoia subject is subject 34 at p.575, about half-way through his entry: "Paranoid."

...That was subject 34. The next, 35 - if I might invite your Lordship to go to subject 42, there had been only three entries which are not in italics at the beginning of section 42, so we see that those three entries:

Day 7, ringing in ears, day 17, withdrawal feeling in

afternoon, day 17, blurred vision.

That had been in the original technical report. We notice as to the explanation which Mr. Gray [counsel for Upjohn] opened yesterday about how Mr. Hampton downed tools and that with subject 42, he did pick up three, but not all, of the medical event entries for subject 42 before he downed tools, making the assumption that he had downed tools after day 17 of that patient, because everything after that is in italics. Subject 42 exhibits a panoply of symptoms so troubling, so continuous and so long as to make one anxious about him, granted that he never has his dose reduced.

...My Lord, I paused on subject 42 and had yet to mention two new paranoidias: subject 45, p.579:

Day 44, paranoid feelings.

The last subject in this group, subject 47, p.580 at the top:

Day 21, paranoid.

So now, instead of two triazolam subjects exhibiting paranoia and two placebo subjects exhibiting paranoia, as we had it from the 1973 technical report, it is on the face of the document seven triazolam subjects with 1mg with paranoia, as against two on placebo. At p.582, C6, we have the like information for the placebo group and the position there about paranoia remains unchanged.

Day 17, p.46

Mr. Shaw: ...are you aware that paranoia in triazolam subjects was underreported by Upjohn?

Dr. Oster, employee of Upjohn: No, I'm not aware of it.

Q. You did not know that?

A. I beg your pardon?

Q. You do not know that? Do you not know that although the 1973 technical report reports two triazolam subjects with paranoia and two placebo subjects with paranoia, it has had to be revised and Upjohn now accepts that there were seven triazolam subjects with paranoia and still just the two on placebo? Do you not know of that?

A. Yes I do, yes.

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Sir Anthony (Mr. Justice) May, in his Judgment at p. 56.:

It is factually correct and undisputed that there were wholesale omissions of medical events from the 1973 P321 Technical Report...The main omissions are from Tables IV and VI (B/198,202) of the 1973 Technical and the scale of the

omissions may be seen by comparing those tables with equivalent tables in the Revised Technical Report (S1/690,69U) prepared under the direction of Dr. Starz in 1991 where the omissions are shown in italics. In addition to apparently random but large scale such omissions, Table VI in the 1973 Report stops completely at Day 17 for subject 42 and omits all entries for subjects 43 and 47 who ought also to have appeared in that table.

"These findings not seen elsewhere."

This statement was used often by Upjohn to mislead regulatory authorities and investigators whenever a serious concern arose regarding a specific adverse reaction from Halcion or regarding its overall safety.

Mr. D. Eady: Do you see the question at the top of the page:

Q: Were the kinds of side effects reported in Holland seen in US clinical trials?

A: No. In fact, side effects of the frequency and severity alleged in Holland have been seen nowhere else in the world....

Is that true?

Dr. M.N. Graham Dukes, former Dutch Health Regulator: That is not true.

Q. Do you remember my learned friend Mr. Gray yesterday asking you about that letter you sent or article you sent to the British Medical Journal in August 1991 which in the event was not published?

A. I do.

Q. Were you angry?

A. Let me put it this way, I was entirely neutral as regards the Halcion history throughout the eighties because it was a mystery in the past for which we had no explanation. It seemed a paradox that these serious effects clearly had occurred in Holland yet we had a statement that they had not been seen earlier, so I had no reason to be angry at that time. I became extremely indignant when in 1990 I was shown the material adduced in the Grundberg case and realised that our drug regulatory agency ten years earlier had been deceived and lied to.

A
HHS Food and Drug Administration
Detroit District

Grand Rapids Resident Post

616 456-2340

Date: March 26, 1993

Subject: Upjohn Halcion Investigation
Newsweek Magazine-Geoff Cowley

TO: MIKE ERSPAMER

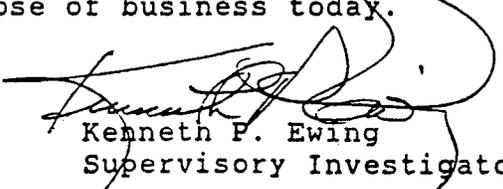
The investigation and various contacts by Cowley have captured the attention of a lot of people. I am attaching for your information two messages I received from Carl Reynolds on the matter.

Please prepare a comprehensive memorandum describing the events that bring us up to today's date. In the memo describe what led to the decision (if that is a correct interpretation) to not write an EIR. Summarize and attach copies of all memoranda that were written. Identify who made critical decisions, what those decisions were, and when they were made. Attach copies of any documents that you have or can obtain.

Include a brief summary of the major findings of the investigation and the evidence that was developed. Attach any pertinent documents. This is not an instruction to repeat what has already been done but merely to summarize so that people who have not read the documents will have a knowledge of the matter.

Describe in detail any phone conversation(s) you have had with Cowley. If any documents were provided to him, attach copies. Include dates of all contact(s).

This assignment must take precedence over everything else. Please have a final response prepared before close of business today.


Kenneth F. Ewing
Supervisory Investigator

cc: KPE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date: March 26, 1993

From: D.M. Erspamer

Firm: The Upjohn Co.
Kalamazoo, MI

Subject: Halcion Investigation/
Geoff Cowley Inquiries

To: Kenneth P. Ewing

The following is a response to Ken Ewing/Mike Erspamer memo dated 3-26-93 requesting a memo of my phone conversation with Geoff Cowley and a recap of the Halcion investigation with explanation of why an EIR was not written.

On 3-19-93 I received a phone call from Geoff Cowley, reporter for Newsweek magazine. Mr. Cowley stated that he was calling in reference to the Halcion investigation. he identified himself as the author of the original Newsweek article of August 19, 1991 regarding Halcion. I recognized his name. He wrote two subsequent articles dated 2-17-92 and 5-25-92. Copies of all three articles are attached to this memo as Attachments 1-3.

He said he had read in the newspapers that the investigation had been closed out and that he had filed an FOI request for FDA's report a month ago, and had not received anything. He was told by the FOI office to call the FDA field office.

Detroit

3-26-92

Carl Reynolds

The investigation was terminated and Upjohn notified verbally and in writing that FDA planned no further action on/about 11-19/12-1-92.

Mike Erspamer was specifically directed to discontinue his investigation on 3-17-92 and told not to collect documents previously requested of Upjohn.

Geoff Cowley contacted Erspamer on 3-19-93 and, in response to a question, was told a report had not been written. During that conversation Mike confirmed the investigation was concluded. No documents were supplied to Cowley.

O: Det 119 11501

Halcion Investigation/Geoff Cowley Inquiries
Page 2

He asked me who he should write to to get a copy of the report. I told him that a final report had not been written. He then asked whether I could confirm that the investigation had been closed out, and I said, yes it had been closed out. He asked whose decision it was to close it out and I said that I didn't know, but that it had been thoroughly discussed by all headquarters people involved. He asked whether I was the field person involved in the investigation and I said that I was. He asked who was in charge of the investigation and I told him that originally it was Don Kilburn but that Kilburn had retired and George Prager had assumed that responsibility.

We talked briefly about the Kansas City law suit (Nila Wacaser case) and he told me that he had interviewed William Barry (ex-Upjohn employee who testified in the case) but that Barry was reluctant to tell him anything. He said that the transcript of Barry's testimony, 800 pages, is now circulating, and that a New York lawyer, Stewart Wexler, had relied on Barry's testimony in a class action suit.

He asked me if I could provide him with any documentation that the investigation had been closed out. He told me that the only documents he had were the Upjohn press release and a letter from Ross Laderman. I told him he could request that information under FOI. That concluded our conversation. I did not provide Mr. Cowley with any documents.

When I returned from two days leave on 3-25-93 I had two phone messages from George Prager and Ken Ewing told me that Theresa Hoog, Office of Public Affairs, had called re. Mr. Cowley's contacts with headquarters personnel and asked that I call her. I called her and told her that Mr. Cowley had telephoned me last Friday re. the Halcion investigation. I then returned George Prager's calls. George told me that Mr. Cowley had set up an interview with Paul Vogel, to be conducted on 3-26-93, and that he (George) was gathering some documents for him. He asked me to FAX him the 2-4-93 memo from Dan Michels, which "closed out" the investigation, and I did so. George stated that he had received a phone call from Mr. Cowley, and wondered where he had gotten his name. I explained that Cowley had called me, and that I had mentioned his (George Prager's) name in the conversation.

To recap the Halcion investigation, following are the pertinent dates:

- 11-18-91: The investigation was initiated, with a briefing and review in Parklawn, room 10B19
- 11-19/20-91: Interview Dan Sigelman, Atlanta

Halcion Investigation/Geoff Cowley Inquiries

Page 3

12-3/4-91: Meeting in Rockville to discuss the investigation
12-9/13-91: Inspection at Upjohn
12-18/19-91: Interview Dr. Rudzik, Wayne, NJ
12-23-92: Visit Upjohn
2-10-92: Visit Upjohn
2-10-92: Interview Dr. Oster, Jackson, MI
2-11-92: Interview Dr. Barry, Kalamazoo, MI
2-12-92: Visit Upjohn
3-1/2-92: Interview Dr. Borden, Toronto, Canada
3-3/4-92: Visit Upjohn
3-12/13-92: Interview Dr. Purpura, Wallingford, CT
3-17-92: In a conference phone call with headquarters

personnel, I was told to discontinue the investigation at the firm. This directive was issued in spite of the fact that Upjohn had called to tell me that the records we had requested were ready for us to pick up, records that were deemed to be extremely important to the investigation. I specifically requested that we at least be allowed to pick up the records that we had previously requested, before discontinuing the investigation. Dave Haggard was adamant that we should not go back into Upjohn even to pick up records that we had previously requested. This verbal directive was followed by a written directive dated 3-19-92 by Ross Laderman (Attachment 4). At issue apparently was whether we were exceeding our 704 inspectional authority, by gathering evidence which might be criminal in nature. This issue had been brought up by Seth Ray, who had apparently discussed it with Dan Michels and George Prager. The general issue of 704 authority had previously been discussed in a memo from Rick Blumberg to Ron Chesemore, dated 3-31-91 (Attachment 5).

5-12-92: Ad Hoc meeting, Rockville, MD. Attachment 6 is a memo of the ad hoc meeting, by Arvin Shroff. Attachments 7 and 8 are two memos dated 5-12-92 and 5-13-92, Paul Leber to Ross Laderman, concerning the ad hoc meeting.

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Halcion Investigation/Geoff Cowley Inquiries
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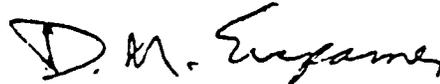
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D.M. Erspamer
Investigator
DET-DO, Grand Rapids RP

DME/dg



Memorandum

G
Date: June 3, 1992
From: D.M. Erspamer
Subject: Options available to us and areas to focus on if we
Resume the Upjohn Halcion Investigation
To: George Prager/Bob Young

BASIS FOR CONTINUING THE INVESTIGATION

From the time that study 321 was conducted and reported (1972-73) to the present time, Upjohn has continued to mislead, manipulate and misrepresent Halcion data to the FDA and to others. The most recent misrepresentation was in February 1992, when Newsweek published an article about Dr. William C. Franklin, a disqualified clinical investigator who had performed a number of Halcion studies, some of them pivotal (protocol 6045 and protocol 6041). Dr. Franklin was disqualified in 1982 and Upjohn was notified by FDA on 11-30-82. Upjohn responded to FDA on 4-7-83, saying that the deletion of Dr. Franklin's data would not change Upjohn's conclusions about safety and efficacy. The letter was a misrepresentation, as it failed to mention protocol 6045, the largest of the pivotal studies conducted by Dr. Franklin. In February 1992 an Upjohn spokesman, Philip Sheldon, told Newsweek that "when we got notification from FDA, we analyzed the safety profile extensively. Franklin's data didn't affect it at all." That statement is false and misleading, and continues Upjohn's pattern of misrepresentations regarding Halcion.

Although it seems clear that Upjohn's actions regarding Halcion were and are criminal in nature, it is also clear that we don't currently have sufficient evidence for a criminal case.

The areas that we could continue to explore, and the people who we could interview to obtain information of a more "material" nature or which would document a clear cut case of conspiracy are as follows:

1. We should explore Upjohn's marketing and promotion of Halcion which appears to be at the heart of the conspiracy to mislead and defraud FDA.
 - A. Upjohn attempted to gain approval of the 1 mg dose and pushed for long term use, even though they knew that 1 mg was too high and that long term use was inappropriate and dangerous. By misrepresenting the safety data, they were able to persuade FDA reviewers to waive the proposed 14 day duration of use limit,

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- B. Review of current inappropriate to recent criminal periods of time. on Halcion for 13 months. Dr. Sidney Wolfe has recently stated (USA Today, 5-28-92) that at least 30% of people taking Halcion have been on it for more than three months.

We may be able to develop evidence that Upjohn actively promoted Halcion for long term use. Upjohn has been involved with promotion of drugs for extra label use in the past, and they have done it through Journal articles as well as verbally through sales representatives. We could visit some psychiatric institutions that have in-house pharmacies, and talk with personnel in purchasing or clinical who normally deal with the drug representatives. We could also talk to doctors who prescribe Halcion and find out what type of "propaganda" was circulated from Upjohn regarding Halcion. We could also send out assignments to other districts to conduct this type of a survey. Some of the doctors who have been outspoken critics of Halcion may be able to provide us with information regarding the promotional practices of Upjohn.

This type of promotion would be in keeping with the firm's recent regulatory history, i.e., promotion of Provera tablets for an unapproved use in 1990 (recalled), five (5) regulatory letters sent to Upjohn's Veterinary Drug division for violative promotional practices in 1990, and investigation of promotion of Micronase and Ansaid in 1991.

*Some of the EX-
Upjohn employees
we interviewed
openly stated that
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key people at Upjohn knew it.*

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interviewed Dr. Barry on 2-11-92 and on 3-3-92 (see memo of interviews). Dr. Barry is critical of the way in which Upjohn handled Halcion - particularly that they tried to suppress the adverse reaction data. Dr. Barry was forced to resign from the company because of his opposition to the way Upjohn was handling Halcion. Other Upjohn employees who were critical of Halcion were also forced out.

In 1984 Upjohn received an inquiry from the French government about Halcion adverse reactions. A draft response was prepared and Dr. Barry reviewed it. He wrote a memo dated 2-16-84 (PX360) in which he stated that the response contained inaccurate data. Dr. Barry never received a response to his memo. The response was supposed to be signed by Al Varley or Mike Bremmer but they refused to sign it, so a corporate decision was made that Robert Purpura would sign it.

Dr. Barry also wrote a memo dated 6-17-99 regarding a response to the Japanese Ministry of Health. Dr. Barry thought the response was misleading in that it omitted important information.

We asked Upjohn for copies of any documents written in response to Barry's memos and the only document obtained was a 3-2-84 memo, D.H. Hodge to T.L. Jones, which discusses Barry's 2-16-84 memo.

From our previous conversations with him, it appears that Dr. Barry has a lot more information that he has not yet shared with us. His deposition in the Kansas City Trial may yield some information, and he may be willing to talk to us again.

- C. Alan B. Varley, M.D. former Upjohn employee (he retired in October 1987). He was one of the Upjohn people forced into an early retirement. We need to ask him about the statement in the 9-10-82 memo, Purpura to Varley: "Al, I cannot go along with the perception that we are lucky Halcion has not been approved here or else we would be in the same boat as Oraflex." Was it Varley that made the comparison with Oraflex, or someone else? Although Dr. Barry characterized Varley as a "company man", he has

important information that may be useful to us. According to Barry, Varley felt that certain things should be in the package insert, and that Dr. Purpura was not doing his job. Dr. Varley is currently listed in the Kalamazoo phone book at 738 E. Full Lake Dr., phone (616)731-5613.

- D. Robert P. Purpura, Bristol-Myers Squibb, Wallingford, CT (previously interviewed on 3-13-92) to discuss the following issues, and others:
- a. What did he mean: "Al, I cannot go along with perception that we are lucky Halcion has not been approved here or else we would be in the same boat as Orflex." (Al is Alan B. Varley). See the 9-10-82 memo, Purpura to Varley, PX243.
 - b. Discuss long-term use of Halcion. In his 8-16-82 memo to Varley (PX240), Purpura stated that "the use of hypnotics beyond two or at most three weeks is rarely, if ever, indicated."
 - c. In the same 8-16-82 memo, Purpura says "...the rebound insomnia issue and the 'scary side effects' issue would disappear, since they are seen almost exclusively with the inappropriate use of Halcion; i.e., long term use..." What did he mean by scary side effects? Was he quoting someone else's statement?
- E. Dr. Judith Jones. Obtain information regarding the specific data that Upjohn supplied her for her "meta analysis" of Halcion, and for her testimony before the advisory panel.
- F. David J. Greenblatt, M.D., Tufts, New England Medical Center, 171 Harrison Ave., Boston, MA 02111. Dr. Greenblatt is the author of an article published in the May 1984 issue of the Journal of Clinical Psychiatry, which indicates that Greenblatt reviewed 45 double blind studies. Study 321 is one of the studies but the article does not refer to any 1 mg studies.
- G. Charles M. Large, former Upjohn employee. Mr. Large was involved in the response from Upjohn to FDA regarding the Franklin studies. He is retired but still lives in the Kalamazoo area. Mr. Large, along

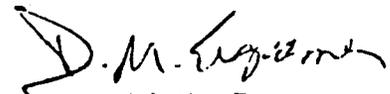
Options available to Us and Areas to Focus on if We
Resume the Upjohn Investigation
Page 6

with Joe Mason (also retired) were involved with data verification and preparation of annual reports for Upjohn.

Other personnel who we might have an interest in talking to are:

Sally Boukema, re. log books on study 321
Veldkamp - re. 321
David D. Gay
Raymond M. DeHaan, M.D. - replaced Varley
Joseph P. Mariano, M.D.
Robert B. Raskin, M.D.
Daniel D. Witcher
Ed L. Schumann, Ph.D., re. Franklin letter
R.J. McCarthy (marketing) - still at Upjohn
Bill Crabbs, FDA
Theresa Wu, FDA

I totally reject the idea, brought up at the ad hoc meeting, that Upjohn somehow, didn't know about the side effects in study 321. The authors of the technical report on study 321 (Veldkamp, Rudzik, and Metzler) had to be aware of the adverse effects, for the following reasons: 1. This was a high dose, long term study designed to define the maximum dose and treatment period. Therefore side effects would have been expected (Purpura admitted this when we interviewed him on 3-13-92). 2. William W. Veldkamp, MRC, along with Allan D. Rudzik, Head, Clinical Research CNS Unit, made visits to the study site on a regular basis. Rudzik was very interested in data, according to Veldkamp, and would study and tabulate data from the case report forms. Dr. Rudzik told us that when case report forms came in, he entered pertinent information into a large format accounting-type log book which he maintained. He also told us that Sally Boukema, a Clinical Research Associate (CRA), also maintained log books on the clinical studies, and that her log books were even more complete than his own. She was described as an obsessive, meticulous record keeper (we requested the log books of Dr. Rudzik and Mrs. Boukamp at Upjohn but were told that they could not be found and must have been discarded).


David M. Erspamer

DME/dg

cc: Det-DO - Sheelin

A
HHS Food and Drug Administration
Detroit District

Grand Rapids Resident Post

616 456-2340

Date: March 26, 1993

Subject: Upjohn Halcion Investigation
Newsweek Magazine-Geoff Cowley

TO: MIKE ERSPAMER

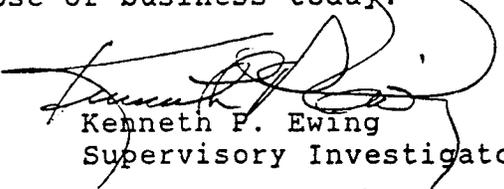
The investigation and various contacts by Cowley have captured the attention of a lot of people. I am attaching for your information two messages I received from Carl Reynolds on the matter.

Please prepare a comprehensive memorandum describing the events that bring us up to today's date. In the memo describe what led to the decision (if that is a correct interpretation) to not write an EIR. Summarize and attach copies of all memoranda that were written. Identify who made critical decisions, what those decisions were, and when they were made. Attach copies of any documents that you have or can obtain.

Include a brief summary of the major findings of the investigation and the evidence that was developed. Attach any pertinent documents. This is not an instruction to repeat what has already been done but merely to summarize so that people who have not read the documents will have a knowledge of the matter.

Describe in detail any phone conversation(s) you have had with Cowley. If any documents were provided to him, attach copies. Include dates of all contact(s).

This assignment must take precedence over everything else. Please have a final response prepared before close of business today.


Kenneth P. Ewing
Supervisory Investigator

cc: KPE



DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

Date: March 26, 1993

From: D.M. Erspamer

Firm: The Upjohn Co.
Kalamazoo, MI

Subject: Halcion Investigation/
Geoff Cowley Inquiries

To: Kenneth P. Ewing

The following is a response to Ken Ewing/Mike Erspamer memo dated 3-26-93 requesting a memo of my phone conversation with Geoff Cowley and a recap of the Halcion investigation with explanation of why an EIR was not written.

On 3-19-93 I received a phone call from Geoff Cowley, reporter for Newsweek magazine. Mr. Cowley stated that he was calling in reference to the Halcion investigation. he identified himself as the author of the original Newsweek article of August 19, 1991 regarding Halcion. I recognized his name. He wrote two subsequent articles dated 2-17-92 and 5-25-92. Copies of all three articles are attached to this memo as Attachments 1-3.

He said he had read in the newspapers that the investigation had been closed out and that he had filed an FOI request for FDA's report a month ago, and had not received anything. He was told by the FOI office to call the FDA field office.

*Detroit
Carl Reynolds*

3-26-92

The investigation was terminated and Upjohn notified verbally and in writing that FDA planned no further action on/about 11-19/12-1-92.

Mike Erspamer was specifically directed to discontinue his investigation on 3-17-92 and told not to collect documents previously requested of Upjohn.

Geoff Cowley contacted Erspamer on 3-19-93 and, in response to a question, was told a report had not been written. During that conversation Mike confirmed the investigation was concluded. No documents were supplied to Cowley.

O: [unclear] 119 115511

[Signature]

Halcion Investigation/Geoff Cowley Inquiries

Page 2

He asked me who he should write to to get a copy of the report. I told him that a final report had not been written. He then asked whether I could confirm that the investigation had been closed out, and I said, yes it had been closed out. He asked whose decision it was to close it out and I said that I didn't know, but that it had been thoroughly discussed by all headquarters people involved. He asked whether I was the field person involved in the investigation and I said that I was. He asked who was in charge of the investigation and I told him that originally it was Don Kilburn but that Kilburn had retired and George Prager had assumed that responsibility.

We talked briefly about the Kansas City law suit (Nila Wacaser case) and he told me that he had interviewed William Barry (ex-Upjohn employee who testified in the case) but that Barry was reluctant to tell him anything. He said that the transcript of Barry's testimony, 800 pages, is now circulating, and that a New York lawyer, Stewart Wexler, had relied on Barry's testimony in a class action suit.

He asked me if I could provide him with any documentation that the investigation had been closed out. He told me that the only documents he had were the Upjohn press release and a letter from Ross Laderman. I told him he could request that information under FOI. That concluded our conversation. I did not provide Mr. Cowley with any documents.

When I returned from two days leave on 3-25-93 I had two phone messages from George Prager and Ken Ewing told me that Theresa Hoog, Office of Public Affairs, had called re. Mr. Cowley's contacts with headquarters personnel and asked that I call her. I called her and told her that Mr. Cowley had telephoned me last Friday re. the Halcion investigation. I then returned George Prager's calls. George told me that Mr. Cowley had set up an interview with Paul Vogel, to be conducted on 3-26-93, and that he (George) was gathering some documents for him. He asked me to FAX him the 2-4-93 memo from Dan Michels, which "closed out" the investigation, and I did so. George stated that he had received a phone call from Mr. Cowley, and wondered where he had gotten his name. I explained that Cowley had called me, and that I had mentioned his (George Prager's) name in the conversation.

To recap the Halcion investigation, following are the pertinent dates:

- 11-18-91: The investigation was initiated, with a briefing and review in Parklawn, room 10B19
- 11-19/20-91: Interview Dan Sigelman, Atlanta

Halcion Investigation/Geoff Cowley Inquiries
Page 3

- 12-3/4-91: Meeting in Rockville to discuss the investigation
12-9/13-91: Inspection at Upjohn
12-18/19-91: Interview Dr. Rudzik, Wayne, NJ
12-23-92: Visit Upjohn
2-10-92: Visit Upjohn
2-10-92: Interview Dr. Oster, Jackson, MI
2-11-92: Interview Dr. Barry, Kalamazoo, MI
2-12-92: Visit Upjohn
3-1/2-92: Interview Dr. Borden, Toronto, Canada
3-3/4-92: Visit Upjohn
3-12/13-92: Interview Dr. Purpura, Wallingford, CT
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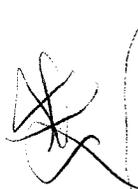
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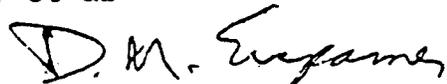
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D.M. Erspamer
Investigator
DET-DO, Grand Rapids RP

DME/dg



Memorandum

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To: George Prager/Bob Young

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prescribed in
supply."

- B. Review of current inappropriate to recent criminal periods of time. on Halcion for 15 months. Dr. Sidney Wolfe has recently stated (USA Today, 5-28-92) that at least 30% of people taking Halcion have been on it for more than three months.

We may be able to develop evidence that Upjohn actively promoted Halcion for long term use. Upjohn has been involved with promotion of drugs for extra label use in the past, and they have done it through Journal articles as well as verbally through sales representatives. We could visit some psychiatric institutions that have in-house pharmacies, and talk with personnel in purchasing or clinical who normally deal with the drug representatives. We could also talk to doctors who prescribe Halcion and find out what type of "propaganda" was circulated from Upjohn regarding Halcion. We could also send out assignments to other districts to conduct this type of a survey. Some of the doctors who have been outspoken critics of Halcion may be able to provide us with information regarding the promotional practices of Upjohn.

This type of promotion would be in keeping with the firm's recent regulatory history, i.e., promotion of Provera tablets for an unapproved use in 1990 (recalled), five (5) regulatory letters sent to Upjohn's Veterinary Drug division for violative promotional practices in 1990, and investigation of promotion of Micronase and Ansaid in 1991.

*Some of the EX-
Upjohn employees
we interviewed
openly stated that
this drug was
totally inappropriate
for long term use, &
key people at Upjohn knew it.*

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interviewed Dr. Barry on 2-11-92 and on 3-3-92 (see memo of interviews). Dr. Barry is critical of the way in which Upjohn handled Halcion - particularly that they tried to suppress the adverse reaction data. Dr. Barry was forced to resign from the company because of his opposition to the way Upjohn was handling Halcion. Other Upjohn employees who were critical of Halcion were also forced out.

In 1984 Upjohn received an inquiry from the French government about Halcion adverse reactions. A draft response was prepared and Dr. Barry reviewed it. He wrote a memo dated 2-16-84 (PX360) in which he stated that the response contained inaccurate data. Dr. Barry never received a response to his memo. The response was supposed to be signed by Al Varley or Mike Bremmer but they refused to sign it, so a corporate decision was made that Robert Purpura would sign it.

Dr. Barry also wrote a memo dated 6-17-99 regarding a response to the Japanese Ministry of Health. Dr. Barry thought the response was misleading in that it omitted important information.

We asked Upjohn for copies of any documents written in response to Barry's memos and the only document obtained was a 3-2-84 memo, D.H. Hodge to T.L. Jones, which discusses Barry's 2-16-84 memo.

From our previous conversations with him, it appears that Dr. Barry has a lot more information that he has not yet shared with us. His deposition in the Kansas City Trial may yield some information, and he may be willing to talk to us again.

- C. Alan B. Varley, M.D. former Upjohn employee (he retired in October 1987). He was one of the Upjohn people forced into an early retirement. We need to ask him about the statement in the 9-10-82 memo, Purpura to Varley: "Al, I cannot go along with the perception that we are lucky Halcion has not been approved here or else we would be in the same boat as Oraflex." Was it Varley that made the comparison with Oraflex, or someone else? Although Dr. Barry characterized Varley as a "company man", he has

important information that may be useful to us. According to Barry, Varley felt that certain things should be in the package insert, and that Dr. Purpura was not doing his job. Dr. Varley is currently listed in the Kalamazoo phone book at 738 E. Full Lake Dr., phone (616)731-5613.

- D. Robert P. Purpura, Bristol-Myers Squibb, Wallingford, CT (previously interviewed on 3-13-92) to discuss the following issues, and others:
- a. What did he mean: "Al, I cannot go along with perception that we are lucky Halcion has not been approved here or else we would be in the same boat as Oraflex." (Al is Alan B. Varley). See the 9-10-82 memo, Purpura to Varley, PX243.
 - b. Discuss long-term use of Halcion. In his 8-16-82 memo to Varley (PX240), Purpura stated that "the use of hypnotics beyond two or at most three weeks is rarely, if ever, indicated."
 - c. In the same 8-16-82 memo, Purpura says "...the rebound insomnia issue and the 'scary side effects' issue would disappear, since they are seen almost exclusively with the inappropriate use of Halcion; i.e., long term use..." What did he mean by scary side effects? Was he quoting someone else's statement?
- E. Dr. Judith Jones. Obtain information regarding the specific data that Upjohn supplied her for her "meta analysis" of Halcion, and for her testimony before the advisory panel.
- F. David J. Greenblatt, M.D., Tufts, New England Medical Center, 171 Harrison Ave., Boston, MA 02111. Dr. Greenblatt is the author of an article published in the May 1984 issue of the Journal of Clinical Psychiatry, which indicates that Greenblatt reviewed 45 double blind studies. Study 321 is one of the studies but the article does not refer to any 1 mg studies.
- G. Charles M. Large, former Upjohn employee. Mr. Large was involved in the response from Upjohn to FDA regarding the Franklin studies. He is retired but still lives in the Kalamazoo area. Mr. Large, along

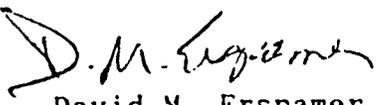
Options available to Us and Areas to Focus on if We
Resume the Upjohn Investigation
Page 6

with Joe Mason (also retired) were involved with data verification and preparation of annual reports for Upjohn.

Other personnel who we might have an interest in talking to are:

Sally Boukema, re. log books on study 321
Veldkamp - re. 321
David D. Gay
Raymond M. DeHaan, M.D. - replaced Varley
Joseph P. Mariano, M.D.
Robert B. Raskin, M.D.
Daniel D. Witcher
Ed L. Schumann, Ph.D., re. Franklin letter
R.J. McCarthy (marketing) - still at Upjohn
Bill Crabbs, FDA
Theresa Wu, FDA

I totally reject the idea, brought up at the ad hoc meeting, that Upjohn somehow, didn't know about the side effects in study 321. The authors of the technical report on study 321 (Veldkamp, Rudzik, and Metzler) had to be aware of the adverse effects, for the following reasons: 1. This was a high dose, long term study designed to define the maximum dose and treatment period. Therefore side effects would have been expected (Purpura admitted this when we interviewed him on 3-13-92). 2. William W. Veldkamp, MRC, along with Allan D. Rudzik, Head, Clinical Research CNS Unit, made visits to the study site on a regular basis. Rudzik was very interested in data, according to Veldkamp, and would study and tabulate data from the case report forms. Dr. Rudzik told us that when case report forms came in, he entered pertinent information into a large format accounting-type log book which he maintained. He also told us that Sally Boukema, a Clinical Research Associate (CRA), also maintained log books on the clinical studies, and that her log books were even more complete than his own. She was described as an obsessive, meticulous record keeper (we requested the log books of Dr. Rudzik and Mrs. Boukema at Upjohn but were told that they could not be found and must have been discarded).


David M. Erspamer

DME/dg

cc: DET-DO - Sheerin