

Department of Health, Education and Welfare
Food and Drug Administration

Recommended Decision and Report
of the
Presiding Officer

Regulatory Hearing in the Matter of the Eligibility of
Abraham A. Chaplan, M.D.
To Receive Investigational-Use Drugs

INTRODUCTION

This matter is before the Food and Drug Administration (FDA) to determine whether Abraham A. Chaplan, M.D., an investigator of new drugs, should be entitled to continue to receive investigational-use drugs. For the reasons given below, it is the recommended decision of the presiding officer that he is no longer entitled to receive investigational-use drugs.

Relevant Statutes and Regulations

Section 355(i) of the Federal Food, Drug and Cosmetic Act (Act) 21 U.S.C. 355(i), authorizes FDA to issue regulations permitting qualified experts to investigate the safety and effectiveness of unapproved new drugs—that is, drugs that are intended solely for investigational use. (The term "new drug" is defined in section 201(p) of the Act, 21 U.S.C. 321(p).) Section 355(i) provides that FDA may establish in such regulations conditions relating to the handling of such drugs that will insure the protection of the public health, including the establishment and maintenance of such records and the making of such reports as will enable FDA to evaluate the safety and effectiveness of such drugs in the event

approval is sought for the drug under section 355 of the Act. Section 355(i) provides that FDA may establish regulations requiring:

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b).

21 U.S.C. 355(i) (3)

The relevant regulations relating to disqualifications of investigators for failure to maintain the required records are found in 21 Code of Federal Regulations § 312.1(c).

(c)(1) Whenever the Food and Drug Administration has information indicating that an investigator has repeatedly or deliberately failed to comply with the conditions of these exempting regulations outlined in Form FD-1572 or FD-1573, set forth in paragraphs (a)(12) and (13) of this section, or has submitted to the sponsor of the investigation false information in his Form FD-1572 or

FD-1573 or in any required report, the Bureau of Drugs will furnish the investigator written notice of the matter complained of in general terms and offer him an opportunity to explain the matter in an informal conference and/or in writing. If an explanation is offered but not accepted by the Bureau of Drugs, the investigator shall have an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to Part 16 of this chapter, on the question of whether the investigator is entitled to receive investigational new drugs.

(2) After evaluating all available information, including any explanation and assurance presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the conditions of the exempting regulations in this section or has repeatedly or deliberately submitted false information to the sponsor of an investigation and has failed to furnish adequate assurance that the conditions of the exemption will be met, the Commissioner will notify the investigator and the sponsor of any investigation in which he has been named as a participant that the investigator is not entitled to receive investigational-use drugs with a statement of the basis for such determination.

The conditions referred to in 21 CFR 312.1(c) ("paragraphs (a)(12) and (13) of this section") provide in relevant part:

6(c) The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.

21 CFR 312.1(a)(12) Form FD-1572

4(c) The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

21 CFR 312.1(a)(13) Form FD-1573

BACKGROUND

By letter of March 9, 1978, the Bureau of Drugs advised Dr. Chaplan that based on an October 19, 1977, inspection of his facilities and methods for the testing of four named investigational-use drugs, the Bureau believed that Dr. Chaplan had repeatedly and deliberately failed to comply with the FDA regulations governing the use of investigational drugs. Dr. Chaplan

was advised specifically that the following matters showed non-compliance with the regulations:

1. A lack of patient records for the study, conducted by Dr. Chaplan for in 1975.
2. A lack of patient records for the study, conducted by Dr. Chaplan for in 1975.
3. A lack of patient records for a recently completed study, conducted by Dr. Chaplan.
4. Study violations in the study as determined by the fragmentary records of 11 patients (inadequate patient medical histories, inadequate documentation of laboratory data, inadequate documentation of starting dates, visit dates and drug accountability).

In its March 9, 1978, letter the Bureau offered Dr. Chaplan an opportunity to explain these matters in an informal conference and/or in writing.

Subsequently such a conference was held in the Bureau of Drugs on April 28, 1978. In addition Mr. attorney for Dr. Chaplan,

submitted written comment on this matter to the Bureau on June 26, 1978.

By letter of September 7, 1978, the Deputy Commissioner notified Dr. Chaplan that the Bureau had found his explanation of the violations (in both the April 28, 1978, informal conference and Mr. communication of June 26, 1978) unresponsive and unacceptable. The Deputy Commissioner's letter notified Dr. Chaplan of an opportunity for a regulatory hearing before the Food and Drug Administration pursuant to 21 CFR Part 16 to determine whether he is entitled to receive investigational new drugs. This letter further advised that the matters to be considered at the regulatory hearing would be those set out in the Bureau's March 9, 1978, letter to him.

By memorandum of September 21, 1978, the Deputy Commissioner designated Mark Novitch, M.D., Acting Associate Commissioner for Health Affairs, to preside at Dr. Chaplan's regulatory hearing. By Notice of Hearing of September 24, 1978, the presiding officer scheduled Dr. Chaplan's regulatory hearing for October 24, 1978. At the request of Counsel for Dr. Chaplan a continuance was granted and by Notice of Hearing of October 18, 1978, the presiding officer rescheduled the hearing for November 15, 1978. The hearing began as scheduled and concluded on the same date.

Two witnesses were called by the Bureau in these proceedings:

Ph.D., a physiologist and biochemist and
M.D., a diplomate, of the American Board of Psychiatry and Neurology. The Bureau in addition introduced seven exhibits into this record.^{1/} Dr. Chaplan did

not testify nor did he call any witnesses in these proceedings. He did, however, introduce 12 exhibits into the record.^{2/} In addition, the presiding officer introduced two exhibits into this record.^{3/}

- 1/ Bureau Exhibit A - Curriculum Vitae of Ph.D,
" " B - Study Records
" " C - Transcript of Dr. Chaplan's April 28, 1978,
Conference with the Bureau of Drugs
" " D - December 13, 1976, Letter from Dr. to
Dr. Chaplan
" " E - August 15, 1978, Action Memorandum from the Bureau
of Drugs to the Commissioner of Food and Drugs
" " F - October 10, 1978, Letter and Attachments from
Mr. to Bureau of Drugs
" " G - Curriculum Vitae of M.D.

- 2/ Chaplan Exhibit 1 - Investigator Guidelines
" " 2 - Geriatric Testing Application Medical History
Questionnaire
3 - August 18, 1976, Letter from Dr. Chaplan to
"Dear Colleague"
" " 4 - Consent Form for Administration of

Chaplan Exhibit 5 - December 18, 1976, Letter from Dr. Chaplan
to Dr.

" " 6 - December 14, 1976, Letter from to
Dr.

" " 7 - February 5, 1977, Letter from Dr. Chaplan to
Dr.

" " 8 - May 24, 1977, Letter from to
Dr. Chaplan

" " 9 - December 13, 1976, Letter from to
Dr. Chaplan

" " 10 - May 26, 1977, Letter from Dr. to
Dr. Chaplan

" " 11 - Statement of Dr. Chaplan's Teaching Schedule at
the Hospital

" " 12 - "Principles and Problems in Establishing the
Efficacy of Psychotropic Agents" (Taken official
notice of by the presiding officer—not admitted)

3/ Presiding Officer Exhibit A - December 27, 1976, Letter from
Dr. to Dr. Chaplan

" " " B - "Diagnostic and Statistical Manual of
Mental Disorders (DSM-11)"

At the conclusion of the hearing the presiding officer ordered the record of the proceedings be held open for a period beyond the receipt of the transcript by the parties for receipt of written submissions. By letter of November 27, 1978, the transcript was provided to counsel for both Dr. Chaplan and the Bureau, and the parties were advised that the record would be closed as of December 14, 1978. Within the time allotted a submission entitled "Memorandum Submitted on Behalf of Dr. Abraham A. Chaplan" was received from Mr. _____ Counsel for Dr. Chaplan, and a submission entitled "Post-Hearing Brief" was received from Mr. Fletcher E. Campbell, Jr., Counsel for the Bureau. Both submissions are included as part of this record.

DISCUSSION

The Need for Records

At issue in this matter is the adequacy of Dr. Abraham A. Chaplan's patient records with respect to his clinical studies on the investigational-use drugs, _____ and _____ The Bureau contends that Dr. Chaplan's records were inadequate to establish patient diagnosis and thus assure proper selection of subjects in these experiments, to provide for adequate patient follow-up and to provide for verification of patient observations.

clinical research governed by FDA regulations it is not possible for these regulations to delineate for each individual situation specifically what records and documentation are required. What the regulations do require is that adequate and accurate patient records that are pertinent to the particular clinical study be maintained by the investigator.

The minimum records essential for scientific evaluation of a particular clinical investigation, however, is fully understood by the scientific community. Dr. [redacted] in his testimony described what constituted an adequate case history and why a case history was essential to the conduct of a clinical investigation, especially a psychiatric or neuropsychiatric investigation (Tr. 115-118). In describing the difference between a case history and a case report (PRF) he stated:

A case report is different from the history, in that it represents a cross-sectional description at a given point in time of a patient who is under treatment or investigation. It's a tiny bit of a history, just like what we're doing now is part of the history of the FDA, because it's a cross-section of one of the things that's happening. A history describes a longitudinal process with all the various cross-sections that make up that longitudinal section, longitudinal strip (TR. 199).

The Study

With respect to Dr. Chaplan's [redacted] study, Dr. [redacted] pointed out the need for case histories for the purpose of establishing the diagnosis and selection of the study population. He stated:

The Bureau contends that such records are not only necessary from the stand-point of patient safety (safe and appropriate treatment) but in addition to establish the reliability and reproducibility of the experiment. The Bureau further contends that with respect of the study there exists discrepancies between the data contained in what patient records that do exist and that contained in the Patient Reports Forms. Dr. Chaplan contends that the case reports (Patient Record Forms or PRFs) are themselves adequate records from the stand-point of clinical investigations and that a clinical investigator has no obligation of maintaining clinical records on subjects of clinical investigations beyond them.

Dr. Chaplan had signed and submitted to the sponsor a Form FD-1573, "Statement of Investigator" for each of the four investigational-use drugs at issue in this hearing (Bureau Exhibit F). Form FD-1573, contained in the Investigational New Drug Regulations (21 CFR 312.1(a)(13)) provides in part:

4(c) the investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

It is, of course, a basic tenet of scientific investigation that documentation be made of all observations. Unsupported and undocumented observations stand alone and as a matter of simple experience are unworthy of scientific credibility. Because of the wide variety of types of

In the study I see not one element of what I would call a history. There are very adequate case reports on the progress of the study. There is a statement on the face sheet about the diagnosis, which assumes the knowledge of historical data, because the diagnosis can't be made without it. But there is no evidence at all of any substantiating documents or data that we have received that could in any way be construed as a history--psychiatric, medical or general (Tr. 121).

I think that especially the study beautifully explicates the utter essentially of the case history, because in no way can a diagnosis of depressive neurosis be made without it (Tr. 122).

The study protocol for (Chaplan Exhibit 1) provides for patient inclusion characteristics "Depressed out-patients with a diagnosis of depressive neurosis (DSM 11/300.4)." The parenthetical reference refers to the "Diagnostic and Statistical Manual of Mental Disorders" Second Edition, prepared by the American Psychiatric Association (Presiding Officers Exhibit B). The definition of depressive neurosis in the manual thus becomes the selection criteria for patients in the study. In this regard in commenting on the absence of case histories for Dr. Chaplan's patients in the study Dr. stated:

Now, on the psychiatric examination of a patient without historical data, you can tell something about depression not everything by a long shot. But you can know that maybe a person is excessively

depressed. But you can't tell if there is an internal conflict, if there has been an identifiable event, unless you ask about events in the patient's past life. Now, it may very well be that all of this data was collected on these patients. But there is no reason to believe that it was ever gotten, except maybe somebody's word. Anybody could have written down "depressive neurosis: yes." (Tr. 125-126)

Further documentation of the need for patient case histories to provide for careful definition of the condition of subjects selected for inclusion in clinical trials can be found throughout the book entitled, "Principles and Problems in Establishing the Efficacy of Psychotropic Agents" (introduced by Dr. Chaplan and taken official notice of by presiding officer (Tr. 174-175)). That Dr. Chaplan considers the book authoritative with respect to clinical investigations of psychotropic agents is evidenced by Mr. [redacted] referral to the book in his cross-examination of both Dr. [redacted] and Dr. [redacted] (Tr. 75-76, 149-153) and most specifically in his closing statement:

Now Doctor, this is a book that's been put out by this Department in 1971. Certainly everybody doing clinical investigative work for this Department has a right to rely on what it says (Tr. 187).

Particularly noteworthy to this point is the introduction to the Chapter of this book from which Mr. [redacted] extensively quoted in his

cross-examination of Dr. (Tr. 149-153). The introduction reads in part (at page 267):

If clinical trials are to be appropriately reviewed and interpreted by government agencies, independent scientists, and clinical researchers and if the most sophisticated statistical procedures are to be utilized, detailed and complete documentation of the procedures employed and the material accumulated during these trials must be easily accessible and as complete as possible.

The data which should be collected and stored must include all details of the protocol, the experimental design, and the normal ranges of laboratory values. In addition, the entire clinical record including the physical description of the patient; the medical and social history; the results of previous therapies; the status of the illness at the start, during, and after the trial; and all the laboratory values determined for each patient should be documented for every clinical trial.

That Dr. Chaplan's records for any of the studies at issue do not even approach the standard quoted above is abundantly clear from the record in these proceedings.

The Study

Dr. Chaplan's clinical study on the drug was terminated by the sponsor prior to its completion because of certain irregularities found in

the Patient Report Forms (PRFs) for this study (Bureau Exhibit D). Examination by Dr. [redacted] of a sampling of the patient records for this study found them to consist of disorganized notes on bits of paper and further that there existed discrepancies between notations in these records and information recorded on PRFs, as to the dates patients entered into the study, previous and concomitant medications received by patients and dates of laboratory analyses (Tr. 33-49, Bureau Exhibit B). Dr.

[redacted] commented extensively on the inadequacies of the [redacted] patient records (Tr. 131-144). In summing up his criticisms of these records he stated:

So the fact that these things weren't filled out, that other patients' or other peoples' names appear on these things, many cryptic comments that are apocryphal and of indeterminate origin, I don't know how they got there, I don't know what they mean—and this is what's meant by a logical sequence. The absence of this, the opposite of this, would be logical; this, you know, is not a logical sequence. It's very disorganized, very disintegrated, very fragmentary, and very difficult to follow (Tr. 138-139).

Irrespective of Mr. [redacted] statement on p. 12 of his post-hearing memorandum: "The [redacted] records were not that good but not that bad," examination of the patient records submitted (Bureau Exhibit B) indicates that they do not reach the threshold of "adequate and accurate case histories" as required by the regulations.

The and Studies

With respect to the and studies, the patient records were reported as lost at the time of Dr. investigation. During this hearing it was brought out that some of the documents relating to the study had been found and were brought to the hearing by Mr.

When the presiding officer asked Mr. if he wanted to introduce these documents into evidence, Mr. stated: "No, I will not introduce them into evidence, for one simple reason: It isn't necessary." (Tr. 185). Since the question of the adequacy of Dr. Chaplan's records with respect to these studies has been raised, either production of these records or in their absence a showing of what these records may consist of so they may be wholly or partially rehabilitated is necessary to answer these questions. It is obvious that in view of Dr. Chaplan's failure to produce any records relating to these studies the presiding officer must conclude that he had not shown that they meet the requirements of the regulation.

The presiding officer wishes to comment only briefly with respect to some of the procedural issues raised in Mr. post-hearing memorandum.

Point I - The Instant Proceeding is Illegal: Counsel for Dr.

Chaplan challenges the proceeding on the basis that an investigation was initiated because of the statements made by a disgruntled employee of Dr. Chaplan's. This matter has no bearing, however, on the facts developed during the ensuing investigation of

his clinical study records. Whether or not Dr. Chaplan was afforded an opportunity to rebut this employee's information, therefore, properly had no bearing on whether this matter would proceed to a regulatory hearing and what the ultimate outcome of that hearing would be. With respect to Dr. Chaplan's convictions for Medicaid fraud, on both occasions when this issue arose during these proceedings, once by Mr. Kean (Tr. 65) and once by Mr. Campbell (Tr. 181), the presiding officer shut-off all discussion as being not relevant to the proceedings. Again the only matters at issue in this proceedings related to the adequacy of Dr. Chaplan's clinical records, and, there was ample evidence in the record to show that these records were inadequate.

Point II - The Procedures Followed at the Hearing are Illegal: The Notice of Opportunity for Hearing issued to Dr. Chaplan in the Deputy Commissioner's letter of September 7, 1978, stated that the matters to be considered at the hearing would be as set forth in the Bureau of Drugs' letter of March 9, 1978. The ruling at the hearing by the presiding officer was that the September 7, 1978, letter would be the governing document (Tr. 10). The fact that the Bureau wished to further restrict its case from the March 9, 1978, specifications could in no way be prejudicial to

Dr. Chaplan. Counsel confuses the notice of hearing (21 CFR 16.24(a)) with the general summary of the information to be presented at the hearing (21 CFR 16.24(d)). The important point is that by virtue of both documents Dr. Chaplan had reasonable notice of matters to be considered at the hearing as required by 21 CFR 16.24(d). Moreover, it is significant that at the hearing, Counsel viewed the "only difference" between the documents as relating to one named patient (Tr. 9-10).

Point III - The Conduct of the Hearing Was Not Fair or Impartial:

The rules governing the conduct of this hearing provide in part that: "No motions or objections relating to the admissibility of data, information and views shall be made or considered" (21 CFR 16.60(c)). Mr. Campbell did make an objection during Mr. cross-examination of Dr. with respect to the termination of the study. The presiding officer did not however, sustain Mr. Campbell's objection. What did occur was that Mr. Campbell anticipated the presiding officer's own objection to the line of questioning as being completely irrelevant to these proceedings. When Mr. was asked to elaborate on how this line of questioning may be relevant he was unable to do so (Tr. 105-106). While the presiding officer instructed both parties with respect to the rules governing the conduct of this hearing, he realized that in spite of these rules and because of their training and experience, counsel for both parties would (and in fact did)

voice objections and make motions. Obviously, the presiding officer has the duty to insure that only relevant matters are presented at the hearing, whether or not in response to an objection from participating counsel.

In sum, none of the procedural points raised by counsel warrants dismissal of these proceedings.

CONCLUSIONS

Consideration of the record in this proceeding requires the conclusions that Dr. Abraham A. Chaplan has repeatedly and deliberately failed to comply with the regulations governing investigational new drugs in that:

1. There does exist inadequate patient records for the study, conducted by Dr. Abraham A. Chaplan.
2. There does exist inadequate patient records for the study conducted by Dr. Abraham A. Chaplan.
3. There does exist inadequate patient records for the study, conducted by Dr. Abraham A. Chaplan.
4. There does exist inadequate patient records for the study, conducted by Abraham A. Chaplan, and further that there are inconsistencies between the patient records that do exist for patients in this study and patient case reports prepared for submission to the sponsor.

RECOMMENDED DECISION

That the Commissioner of Food and Drugs notify Dr. Abraham A. Chaplan that he is no longer entitled to receive investigational use drugs.

1-17-79

Date

Mark Novitch

Mark Novitch, M.D.

Presiding Officer



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

REGISTERED MAIL
RETURN RECEIPT REQUESTED

FEB 28 1979

Abraham A. Chaplan, M.D.
Place

Dear Dr. Chaplan:

Notice of Disqualification to Receive Investigational New Drugs

I have reviewed the record of the regulatory hearing conducted by Dr. Mark Novitch on November 15, 1978, relating to your eligibility to receive investigational-use drugs. At the hearing you were unable to offer satisfactory explanations for the deficiencies observed in your clinical investigations of investigational new drugs as set forth in the September 7, 1978, Notice of Opportunity for Hearing on this matter. Therefore, on the basis of all information, I am affirming and adopting the January 17, 1979, Recommended Decision and Report of the Presiding Officer and have determined that you have repeatedly and deliberately failed to comply with the exempting regulations for new drugs for investigational use in that:

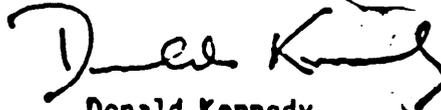
1. Patient records for the study which you conducted are inadequate.
2. Patient records for the study which you conducted are inadequate.
3. Patient records for the study which you conducted are inadequate.
4. Patient records for the study which you conducted are inadequate; further, there are inconsistencies between the patient records that do exist for patients in this study and patient case reports prepared for submission to the sponsor.

Page 2 - Abraham A. Chaplan, M.D.

In accordance with 21 CFR 312.1(c), you are hereby advised that you are no longer entitled to receive investigational new drugs. All such drugs now in your possession should be promptly returned to their supplier.

For your information, enclosed are copies of letters which have been sent to all sponsors of investigations in which you have been named as a participant, notifying them that you are not entitled to receive investigational-use drugs.

Sincerely yours,



Donald Kennedy
Commissioner of Food and Drugs

Enclosures

cc: HF-1 (2)
HF-2
HF-4
HFD-1
GCF-1
HFY-1 R/F
HFY-21 (Chaplan Files)
HFA-225
HFJ-1
HFJ-5 (TRAC #7900473)