DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Ombudsman
5600 Fishers Lane
Room 14B-03, HF-7
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

JAN 1 0 2001

November 22, 2000

H.M. Vriesendorp, M.D., Ph.D.

[redacted]

CERTIFIED MAIL –
RETURN RECEIPT REQUESTED

Ann H. Wion, Esq.[1]
Deputy Chief Counsel
Office of Chief Counsel, GCF-1
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

HAND DELIVERY

Re: Huibert M. Vriesendorp, M.D.
Clinical Investigator Disqualification Hearing

Dear Dr. Vriesendorp and Ms. Wion:

The summary decision and recommendation of the Presiding Officer in the matter of Huibert M. Vriesendorp, M.D. is enclosed. This decision and recommendation will be forwarded to the Commissioner, who will make a final determination whether to disqualify Dr. Vriesendorp from being eligible to receive investigational new drugs, pursuant to 21 C.F.R. § 312.70.

In accordance with 21 C.F.R. § 16.26(c), you may request that the Commissioner review this summary decision. A request for Commissioner's review must be in writing, and delivered to me, at the address provided above, by 4:30 p.m., EST, on January 12, 2001. If you do not submit a request for Commissioner's review by this time, you will be deemed to have waived such review.

Note: You must also deliver a copy of your request for Commissioner's reivew to the opposing party, by the opposing party's close of business on January 12, 2001.

The Commissioner will issue the final determination in this matter after January 12, 2001. If you have any questions about the process, please call me at 301-827-3390.

Sincerely,

Suzanne M. O'Shea
Hearing Coordinator

Enclosure

[1] We understand that the attorneys previously representing the Center for Biologics Evaluation and Research are no longer employed by the Office of Chief Counsel. No notification of re-assignment of this matter has been received. Therefore, this letter is addressed to Ann H. Wion, Esq., Deputy Chief Counsel.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

U.S. FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

HUIBERT M. VRIESENDORP, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

SUMMARY DECISION OF THE PRESIDING OFFICER

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I. INTRODUCTION

As provided in Title 21 of the Code of Federal Regulations ("C.F.R") Parts 16 and 312, I have reviewed:

- the Motion for Summary Decision on all charges, and the supporting exhibits submitted by the Center for Biologics Evaluation and Research ("CBER" or the "Center") ("CBER MSD"),
- the Opposition and exhibits submitted by Huibert M. Vriesendorp, M.D. ("Vriesendorp Opposition"), and
- the Memorandum in Reply submitted by the Center ("CBER Reply") in response to Dr. Vriesendorp's request for a hearing to consider CBER's proposal to disqualify him from being eligible to receive investigational drugs as provided in 21 U.S.C. 355(i) and 21 C.F.R. § 312.70.

I have also considered:

- the Request for Summary Decision on all charges, submitted by Dr. Vriesendorp ("Vriesendorp MSD"),
- the Opposition filed by CBER ("CBER Opposition"), and
- Dr. Vriesendorp's Reply ("Vriesendorp Reply").

As provided in 21 C.F.R. § 16.26(b), this summary decision constitutes my rulings on the Center's Motion and Dr. Vriesendorp's Request.[1] As described in detail below, I find that Dr. Vriesendorp repeatedly and deliberately violated several regulations contained in 21 C.F.R. Part 312. I recommend to the Commissioner that he be disqualified from being eligible to receive investigational new drugs. In accordance with

[1] Dr. Vriesendorp's "Request for Summary Decision" is, in substance, an extension of the arguments made in his Opposition to the Center's Motion for Summary Decision. I have fully considered the arguments made in Dr. Vriesendorp's Request, and in his Reply to the Center's Opposition, in this Summary Decision.

21 C.F.R. §§ 16.95 and 312.70, this decision will be referred to the Commissioner of Food and Drugs, who will make a final determination.

II. BACKGROUND

Huibert M. Vriesendorp, M.D., has since 1988 conducted research with the use of [ ] in the treatment of Hodgkin's Disease patients who have not responded to conventional cancer therapy, i.e., chemotherapy, radiation and in some cases bone marrow transplantation. Dr. Vriesendorp describes the treatment as "... a specific and successful form of [ ] therapy ... [which] provides a delivery system for an 'old' treatment method (radiation) to cancer tissues without indiscriminate delivery of radiation to a patient's healthy tissues."[2]

In late 1990, Dr. Vriesendorp left the employment of [ ] University Oncology Center[3] after having conducted research with [ ] under an investigational new drug application (IND) designated [ ] ("IND [ ]"). The principal investigator for the study, Dr. [ ], issued a letter on October 4, 1990, notifying FDA that Dr. Vriesendorp's participation under the IND had been terminated.[4]

Dr. Vriesendorp moved to the University of [ ] ("[ ]") where, in September 1992, he submitted an IND application to sponsor Hodgkin's Disease research with [ ].[5] Before the study was

[2] Vriesendorp Request for Hearing October 24, 1997, p. 2
[3] Vriesendorp Opposition, p. 26
[4] CBER MSD, Exhibit 10. Dr [ ] stated in the letter that Dr Vriesendorp had, on his own, treated four patients utilizing protocol authorizations from studies other than Dr. Vriesendorp's study.
[5] CBER Opposition, Exhibit 1

initiated, at Dr. Vriesendorp's request[6] the sponsorship was shifted to the [ ] with [ ], M.D. designated as the responsible administrator. Dr. Vriesendorp was listed as the monitor, and as the person responsible for review and evaluation (i.e., the principal investigator). The IND was designated [ ]("IND [ ]) and the study protocol was numbered [ ].[7] The Institutional Review Board for the study was the [ ] Surveillance committee, Office of Protocol Research.[8]

The study under protocol [ ] was titled "Pilot Study of [ ] [ ] in Patients with Therapy Resistant Hodgkin's Disease."[9] Under the protocol, a treatment cycle began with injection of a low dose of [ ] [ ]. The [ ] binds to [ ], which are present in tissues containing Hodgkin's Disease. If a scan by an external camera revealed that the [ ] remained intact and collected in the tumor, a therapeutic dose of [ ] [ ] was administered four to seven days later. The [ ] delivers radiation at the site where it collects. The cycle was repeated with increased therapeutic dosage in five to nine weeks, if blood counts were above specified levels, and specified toxicity was not observed. The cycle was to be stopped if the disease were progressive or stable after two cycles, but would be continued for one full cycle after a complete response was obtained.[10]

The study commenced late in 1992.[11] On March 21, 1995, the [ ] IRB approved a revised protocol, designated [ ], for a new study under IND [ ].[12] The

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[6] Vriesendorp Opposition, Reference 27
[7] Vriesendorp Opposition, Reference 28
[8] CBER MSD, Exhibit 26
[9] CBER MSD, Exhibit 7, p. 1. FDA Establishment Inspection Report (EIR) Narrative. The objectives of the study protocol were "to determine the maximum tolerated activity of [ ] [ ], to determine in vivo distribution and pharmacokinetics of [ ] [ ] and to compare it to [ ] for prediction of dosimetry and to determine the anti tumor activity of [ ] and [ ]." Id.
[10] CBER MSD, Exhibit 25, Consent Form and Exhibit 26, Protocol [ ]
[11] Vriesendorp Opposition, p. 17

IND submission, dated the same day, listed [ ], M.D. as the responsible administrator; Dr. Vriesendorp continued as monitor and principal investigator.[13] The study title was "Fractionated [ ] Therapy for Patients With Recurrent or Persistent Hodgkin's Disease."[14]

The FDA placed a clinical hold on IND [ ] in October 1995.[15] In January 1996 [ ] notified FDA that after a preliminary audit it had, among other things, closed all studies associated with IND [ ] to new patient entry, placed the IND on permanent hold, and suspended Dr. Vriesendorp's clinical research privileges.[16] Dr. Vriesendorp subsequently left [ ] for employment at the [ ] Cancer Center.

III. PROCEDURAL HISTORY

FDA conducted an inspection of IND [ ] April 8-12, 1996,[17] issuing a Form FD-483 at the conclusion of the inspection. Dr. Vriesendorp replied to the FD-483 in a letter dated April 21, 1996.[18] FDA issued a warning letter dated November 19, 1996.[19] On March 28, 1997, Dr. Vriesendorp responded to the warning letter in writing,[20] forgoing the opportunity for an informal conference pursuant to 21 C.F.R. § 312.70(a). CBER concluded that Dr. Vriesendorp's written explanations were unacceptable

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[12] CBER MSD, Exhibit 17, [ ] memo approving the revised protocol

[13] Vriesendorp Opposition, Reference 28. (Dr. Vriesendorp denominated both the October 1992 and March 1995 IND submissions as Reference 28).

[14] CBER MSD, Exhibit 7, p. 1. The objectives of this clinical study were "to determine early and late side effects to fractionated [ ] and to determine response rate and duration in patients with recurrent or persistent Hodgkin's disease after fractionated [ ]." Id.

[15] Vriesendorp Opposition, Reference 41. The hold was initiated because of questions about the manufacturing of the test article and because of deficiencies in the protocol of another of Dr. Vriesendorp's studies.

[16] CBER MSD, Exhibit 6, [ ] letter to FDA.

[17] The Narrative Summary of the Establishment Inspection Report is Exhibit 7, CBER MSD

[18] CBER MSD, Exhibit 5

[19] CBER MSD, Exhibit 1

[20] CBER MSD, Exhibit 2

because they failed to adequately address the violations. Therefore, on September 19, 1997, the FDA Associate Commissioner for Regulatory Affairs issued a Notice of Opportunity for Hearing (NOOH) under 21 C.F.R. Part 16 to determine whether Dr. Vriesendorp should be disqualified from receiving investigational drugs.[21] Briefly, the charges and the relevant regulations were as follows:

Charge 1 – failure to submit an Investigational New Drug Application (IND) to FDA and failure to withhold administration of an investigational new drug until an IND was in effect (21 C.F.R. §§ 312.20, 312.40(d) and 312.50), specifically administration of [ ] in place of [ ]

Charge 2 – failure to fulfill the general responsibilities of an investigator (21 C.F.R. § 312.60) by deviating from the protocol for the study; this charge includes seven subcharges.

Charge 3 – failure to ensure initial and continuing review and approval by an Institutional Review Board (21 C.F.R. §§ 56.103(a) and 312.66) by failing to report certain deaths and adverse reactions.

Charge 4 – failure to maintain adequate and accurate records relating to the investigational drugs (21 C.F.R. §§ 312.60 and 312.62(a)).

Charge 5 – failure to prepare and submit investigator reports (21 C.F.R. § 312.64) by failing to report certain adverse reactions.

Charge 6 – failure to obtain informed consent in accordance with the provisions of 21 C.F.R. Part 50 and 21 C.F.R. § 312.60, because of misleading statements in the consent form.

[21] CBER MSD, Exhibit 3

Dr. Vriesendorp submitted his Request for Hearing on October 24, 1997. CBER filed its Motion for Summary Decision on May 14, 1999. Dr. Vriesendorp submitted his Opposition June 8, 1999 and CBER filed its Reply June 24, 1999. Dr. Vriesendorp also submitted a Request for Summary Decision on May 13, 1999 (Designated "Vriesendorp MSD" in this Summary Decision). CBER filed its Opposition on June 8, 1999, and Dr. Vriesendorp submitted his Reply on June 23, 1999.

Dr. Vriesendorp has raised the issue of discovery in this proceeding. He stated that he submitted a Freedom of Information (FOI) request in 1996 and another in 1997 in an effort to learn all relevant facts, but he never received any response.[22] No documentation of a 1996 or a 1997 FOI request is included in the record of this proceeding. However, Dr. Vriesendorp submitted a copy of letter from the CBER Freedom of Information Office, dated October 18, 1999, referring to an April 9, 1999 FOI request.[23] This letter indicates that Dr. Vriesendorp received 1,229 pages of information. According to Dr. Vriesendorp, CBER determined that another 255 pages were not releaseable.[24] Because of the withheld 255 pages, Dr. Vriesendorp argues that discovery is incomplete.[25]

I have concluded that the 255 withheld pages should not delay this proceeding Dr. Vriesendorp has access to all the documents CBER relies on in this matter, as they are attached to CBER's motion for summary decision, response, and reply. Moreover, Dr. Vriesendorp has been able to produce a large number of documents on his own; he filed 85 references with his Opposition, and 30 exhibits with his Request for Hearing.

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[22] Vriesendorp Opposition, p. 54

[23] See the October 18, 1999 letter from Jamie Natour, FDA, to Dr. Vriesendorp, attached as Exhibit 1 to this Summary Decision.

[24] See the November 9, 1999 letter from Dr. Vriesendorp to Jamie Natour, FDA, attached as Exhibit 2 to this Summary Decision. This letter requested the withheld 255 pages, but as of the date of this Summary Decision, the agency has not responded.

[25] See the November 9, 1999 letter from Dr. Vriesendorp to Dr. Linda Ann Sherman, the previous Presiding Officer in this matter.

More significantly, he does not specify particular documents that he believes he needs in order to respond to specific charges; nor does he explain how such documents would be helpful. Thus, it appears that Dr. Vriesendorp already has all the information he needs. Therefore, I am now proceeding with this summary decision.

IV. STANDARD FOR SUMMARY DECISION

Under 21 C.F.R. § 16.26(b), the Presiding Officer is authorized to issue a summary decision on any issue in the hearing if the Presiding Officer determines from material submitted in connection with the hearing, or from matters officially noticed, that there is no genuine and substantial issue of fact respecting that issue. A summary decision may be issued any time after FDA receives a request for a hearing in response to an NOOH.[26] The standard for administrative summary decision contained in 21 C.F.R. § 16.26(b) mirrors that contained in Rule 56 of the Federal Rules of Civil Procedure ("Fed.R.Civ.P."), which provides that summary judgment "shall be rendered ... if ... there is no genuine issue as to any material fact and ... the moving party is entitled to a judgment as a matter of law." Fed.R.Civ.P. 56(c). Therefore, the Presiding Officer may be guided by the body of law developed under Rule 56 in determining whether summary decision is warranted.[27]

The party moving for summary judgment bears the burden of establishing the absence of a genuine issue of material fact. *Adickes v. S.H. Kress*, 398 U.S. 144, 157

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[26] For the purposes of 21 C.F.R. § 16.26(b), a hearing commences upon receipt by FDA of a request for a hearing submitted under 21 C.F.R. § 16.22(b).

[27] *John D. Copanos and Sons, Inc. v. FDA*, 854 F.2d 510, 523 (D.C Cir. 1988) (finding that the principles of *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 247-248 (1986) "apply with equal force in the context of administrative judgment."). *See* also 53 *Fed. Reg.* 4613, 4614 (February 17, 1988)(stating that the standard for summary decision set forth in 21 C.F.R. § 16.26 "conforms to well-settled law.");and *Puerto Rico Aqueduct and Sewer Authority v. EPA*, 35 F.3d 600, 604-608 (1st Cir. 1994) (finding that "[f]rom its inception, the concept of administrative summary

(1970). A party opposing a properly supported motion for summary decision has the burden of showing that a rational trier of fact could find for the nonmoving party and thus that there is a "genuine issue for trial." *Matsushita Electrical Indus. Co. v. Zenith Radio Corp.*, 475 U.S. 574, 586 (1986). Any doubts are to be resolved in favor of the non-moving party and the non-moving party is entitled to all justifiable inferences. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255 (1986). To fulfill this burden, the nonmoving party "must set forth specific facts showing that there is a genuine issue for trial." Fed.R.Civ.P. 56(e); *Matsushita Electrical*, 475 U.S. at 586; *First Nat'l Bank v. Cities Service Co.*, 391 U.S. 253, 289 (1968).

The mere existence of a scintilla of evidence in support of the non-moving party's position will be insufficient to overcome a motion for summary judgment. *Anderson*, 477 U.S. at 252. Further, the opposition to a properly supported motion for summary judgment "must do more than simply show that there is some metaphysical doubt as to the material facts," *Matsushita Electrical*, 475 U.S. at 586, and cannot rest on mere allegations. *First Nat'l Bank*, 391 U.S. at 289.

V. REGULATORY FRAMEWORK

FDA's regulations governing the clinical evaluation of investigational new drugs, such as those that were administered by Dr. Vriesendorp, are set forth in 21 C.F.R. Part 312. Section 312.70 of the regulations provides for the disqualification of clinical investigators for violations of these regulations:

> After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part

judgment has been linked inextricably to Fed.R.Civ.P. 56," and that "[m]any agencies habitually look to Rule 56 case law for guidance in respect to administrative summary judgments.").

> 50, or Part 56 of this chapter, or has deliberately or repeatedly submitted false information to FDA or to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

21 C.F.R. § 312.70(b). Since CBER's allegations do not relate to the submission of false information to FDA or the sponsor, this proceeding is concerned only with whether Dr. Vriesendorp repeatedly or deliberately failed to comply with the requirements of 21 C.F.R. Parts 50, 56, or 312.

FDA has long interpreted the word "repeatedly," as used in 21 C.F.R. § 312.70, to mean more than once.[28] The term "deliberate" has a specific meaning in the context of 21 C.F.R. § 312.70(b). As stated in the *Report of the Presiding Officer, In the Matter of John H. Hopkinson III, M.D.* (1982), at 10:

> In the context of 21 C.F.R. Part 312, a deliberate action is a willful action that need not entail knowledge that it is a violation of law as long as there is some perception of wrongdoing or of reckless disregard for obvious or known risks... Based on the purpose of the regulation, i.e., to protect patients and the quality of drug research by assuring that deviations from the regulations do not occur ... it is... appropriate to interpret "deliberately" to encompass violations of the regulations that are in "reckless disregard" of the regulations' requirements.

VI. DISCUSSION

The Center and Dr. Vriesendorp have both requested summary decision on all six charges that were included in the NOOH. Three of these charges (charges 2, 3 and 6) have subcharges, one of which (charge 2) has seven subcharges. Although Dr. Vriesendorp requested summary decision on all charges, many of his arguments appear

[28] See, e.g. Reports of the Presiding Officer: *in the Matter of Chaovanee Aroonsakul, M.D.* (1990), (findings adopted by the Commissioner, 1990); *In the Matter of Ronald R. Fuller, D.V.M.* (1987), (findings adopted by the Commissioner 1988); *In the Matter of Stephen Steen, M.D.* at 25 (1982) ("I do not interpret the term, 'repeated,' to require proof of violations in two different studies"). (findings adopted by the Commissioner, 1984); *In the Matter of John H. Hopkinson III, M.D.* (1982), (findings adopted by the Commissioner, 1983); and *In the Matter of Michael C. Gelfand, M.D.* (1980), (findings adopted by the Commissioner, 1981).

to affirmatively assert the existence of a genuine issue of material fact. Where there is a genuine issue of material fact, summary decision must be denied, whether or not a party is representing himself, *pro se*. Accordingly, where I find the existence of a genuine issue of material fact, I have denied both the Center's and Dr. Vriesendorp's motion for summary decision.

I have concluded that there are no genuine issues of material fact for a hearing, and that CBER is entitled to judgment as a matter of law on the following charges, discussed in detail in subsection A of this decision, below, beginning on page 11.

Charge 1 – Administration of L] Without an IND

Charge 2a – Protocol Violation, Patient Eligibility Criteria

Charge 2b – Protocol Violation, Platelet Level Stopping Criteria

Charge 2c – Protocol Violation, Concurrent Therapy

Charge 2f – Protocol Violation, Safety Testing.

I have concluded that there are no genuine issues of material fact for a hearing, and that Dr. Vriesendorp is entitled to judgment as a matter of law on the following charge, discussed in detail in subsection B of this decision, below, beginning on page 27.

Charge 2e – Protocol Violation, Porcine Imaging Study

I have concluded that genuine issues of material fact for a hearing remain for the following charges, discussed in detail in subsection C of this decision, below, beginning on page 28.

Charge 2d – Protocol Violation, Fractionated Dosing

Charge 2g – Protocol Violation, Dosimeter Calculations

Charge 3a – Failure to Report Patient Deaths to the IRB

Charge 3b -- Failure to Report Adverse Reactions to the IRB

Charge 4 – Failure to Maintain Adequate Records

Charge 5 -- Failure to Submit Adverse Reactions to Sponsor

Charge 6a – Informed Consent, Low Blood Cell Counts

Charge 6b – Informed Consent, Safety Testing

Finally, subsection D of this decision, on page 38, addresses an issue raised by Dr. Vriesendorp that does not relate to specific charges, but was presented by Dr. Vriesendorp in opposition to the Center's Motion for Summary Decision.

A. Summary Decision Granted to CBER

Charge 1 -- Administration of [ ] Without an IND

The Center charged that Dr. Vriesendorp administered [ ] [ ] to subject 153743, under IND [ ], on October 14, 1993, without having an IND in effect permitting use of this investigational drug.[29] Clinical studies that were the subject of IND [ ] were limited to the administration of [ ].[30] The Center alleged that Dr. Vriesendorp violated 21 C.F.R. §§ 312.20, 312.40(d) and 312.50[31] by failing to submit an IND to FDA, and failing to withhold administration of an investigational new drug until an IND is in effect.

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[29] CBER MSD, p. 8, and Exhibit 3, NOOH, p. 2

[30] CBER MSD, p. 8

[31] CBER MSD, Exhibit 3, NOOH, p. 2.

21 C.F.R. § 312.20 Requirement for an IND.

(a) A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to § 312.2(a).

(b) A sponsor shall not begin a clinical investigation subject to § 312.2(a) until the investigation is subject to an IND which is in effect in accordance with § 312.40.

(c) A sponsor shall submit a separate IND for any clinical investigation involving an exception from informed consent under § 50.24 of this chapter. Such a clinical investigation is not permitted to proceed without the prior written authorization from FDA. FDA shall provide a written determination 30 days after FDA receives the IND or earlier.

Dr. Vriesendorp admits that he administered the [ ] to subject 153743[32] because the patient developed [ ] to the [ ].[33] However, he claims that he did so under the erroneous assumption that he could still administer the [ ] under IND [ ] administered by Dr. [ ] of [ ] University (the [ ] IND).[34] Dr. Vriesendorp claims that he was never notified by Dr. [ ] that he had been removed from IND [ ] as investigator,[35] and that Dr. [ ] did not request return of the [ ] material.[36] Therefore, Dr. Vriesendorp asserts, his administration of the drug contrary to the protocol of IND [ ] was not deliberate.[37]

Dr. Vriesendorp relies on two letters to support his position. The first, dated September 5, 1990 is from [ ] Ph.D., at [ ] (the "[ ] letter") to Dr. [ ], then at the University of [ ]. Dr. [ ] later became a subinvestigator in the studies covered by IND [ ] at [ ][38] In the letter,

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21 C.F.R. § 312.40 General requirements for use of an investigational new drug in a clinical investigation.

(d) An investigator may not administer an investigational new drug to human subjects until the IND goes into effect under paragraph (b) of this section.

21 C.F.R. § 312.50 General responsibilities of sponsors.

Sponsors are responsible for selecting qualified investigators, providing them with the information they need to conduct an investigation properly, ensuring proper monitoring of the investigation(s), ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND, maintaining an effective IND with respect to the investigations, and ensuring that FDA and all participating investigators are promptly informed of significant new adverse events or risks with respect to the drug. Additional specific responsibilities of sponsors are described elsewhere in this part.

[32] CBER MSD, Exhibit 2, p. 2 ("it seemed natural to use [the [ ] product"); Exhibit 5, p. 1 ("This [ ] product] administration is fully documented in the patient chart.")

[33] CBER MSD, Exhibit 5, p. 1

[34] Vriesendorp Opposition, p. 32

[35] Vriesendorp MSD, p. 4

[36] Id.

[37] Dr. Vriesendorp's denial of deliberateness in the sections of his filings that cover the [ ] is by implication, i.e. he states that he made an "erroneous assumption." Elsewhere in his filings he states that none of his violative actions was deliberate, e.g. Vriesendorp Opposition, pp. 5, 21.

[38] Vriesendorp MSD, Appendix 1, cited in Vriesendorp Opposition, p. 32.

Dr. [ ] states that he was looking forward to continued collaboration with Dr. [ ] would send [ ], and would send additional [ ] as needed.

The second letter, dated April 19, 1996, is from [ ], D.Sc., at [ ] [ ], to FDA (the [ ] letter").[39] In it, Dr [ ] states that he had no record or memory of shipment of [ ] to Dr. Vriesendorp at [ ] The letter does state that there was research collaboration with Dr. Vriesendorp and Dr [ ] in 1993 but that this collaboration did not involve transfer of any [ ] stocks. Dr. Vriesendorp argues that the letter supports his position that Dr [ ] did not destroy [ ] stocks or inform investigators that his IND and [ ] were no longer available.[40]

Dr. Vriesendorp also claims that the [ ] dose he administered was a [ ] dose, not a therapeutic dose, and was without risk, suggesting that an IND would not be necessary for a [ ] dose.[41]

CBER responds that Dr. Vriesendorp's claim that he was unaware that he was no longer authorized to treat patients under IND [ ] is highly implausible because he had left [ ] three years earlier. The Center argues that Dr. Vriesendorp's assertion is disingenuous at best, most likely a post hoc rationalization for conduct he knew was violative.[42]

The Center further argues that administration of the [ ] drug contrary to the provisions of IND [ ] was deliberate[43] because Dr. Vriesendorp was author of the protocol for IND [ ],[44] because Dr. [ ] had notified FDA three years before administration of the [ ] that Dr. Vriesendorp's involvement under IND

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[39] CBER MSD, Exhibit 22
[40] Vriesendorp Opposition, p. 32
[41] Id.
[42] CBER Reply, pp. 6-7

1616 had been terminated,[45] and because Dr. [ ] later reported that he had not authorized clinical use of [ ] material at any site other than [ ].[46]

I first conclude that at the time of administration of [ ], Dr. Vriesendorp clearly intended that the dose be therapeutic.[47] Dr. Vriesendorp appears to have made a post-hoc recalculation, concluding that the dose was actually less than therapeutic.[48] Even if the [ ] dose he administered was a [ ] dose, it still would have been an investigational new drug subject to regulation under 21 C.F.R. Part 312.

I conclude further that Dr. Vriesendorp knew or should have known that there was no IND in effect covering the administration of [ ]: Dr. Vriesendorp did not submit any credible evidence raising a genuine issue of fact that he believed the article was administered under the [ ] IND, or that he had a good faith basis for believing that he was authorized to administer the drug under IND [ ] Neither of the two letters Dr. Vriesendorp relies on (the [ ]" and "[ ]" letters) refers to IND [ ] or otherwise supports a credible argument that Dr. Vriesendorp was authorized to administer the drug under that IND. His failure to ascertain whether administration of [ ] was covered by any IND at a minimum demonstrates a reckless disregard for the regulations' requirement that an IND be in effect before administering an investigational new drug.

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[43] CBER MSD, pp. 9-11

[44] Technically "Study Chairman." CBER MSD, Exhibit 26, protocol 92-001.

[45] CBER MSD, Exhibit 10

[46] CBER MSD, Exhibit 11, Letter from Dr. [ ] to FDA April 19, 1996

[47] See CBER MSD, Exhibit 13 and CBER MSD, Exhibit 5, p. 2. For example, Exhibit 13, Dr. Vriesendorp's clinic notes, states that after rapid elimination of the [ ] occurred "we ... elected ... to give the patient [ ] of [ ] per kg with the option of giving him the additional [ ] the next morning if he showed some blood half life." This dosage is consistent with the protocol's therapeutic dosage, see CBER MSD Exhibit 26, Section 5.0.

[48] In his Opposition, p. 32, Dr. Vriesendorp refers to the discovery of a calibration error and states that "Vriesendorp feels justified in calling this a [ ] *dose without risks*." (Italics in original.) He did not use the "[ ]" defense in any of his earlier documents.

Other evidence in the record also undermines the credibility of Dr. Vriesendorp's argument. For example, Dr. Vriesendorp offered conflicting explanations as to the source of the [ ] In his 1996 letter responding to the FDA inspection, he stated that "by telephone I requested a single ampule of [ ] from old collaborators at [ ]."[49] However, he attached the [ ] letter to his 1999 Motion for Summary Decision, claiming that the letter supports his argument that the material was transferred from [ ] "to Dr. [ ] and myself,"[50] adding in his Opposition that "later [ ] brings [ ] with him [to [ ]]."[51]

I find that Dr. Vriesendorp raised no genuine issues material fact for a hearing on Charge 1. I conclude that Dr. Vriesendorp deliberately violated 21 C.F.R. §§ 312.20 and 312.40(d)[52] by administering [ ] when no IND was in effect, and therefore, that CBER is entitled to judgment as a matter of law.

Charge 2 – Protocol Violations

The Center charged Dr. Vriesendorp with seven violations (subcharges) of 21 C.F.R. § 312.60. That regulation requires the investigator to ensure that the investigation is conducted in accordance with the investigator statement (Form FDA 1572),[53] the investigational plan and applicable regulations; it also requires the investigator to protect the safety and welfare of the subjects.[54] Form FDA 1572 requires

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[49] CBER MSD, Exhibit 5, p. 2
[50] Transmittal letter for Vriesendorp MSD, p. 1
[51] Vriesendorp Opposition, p. 32
[52] CBER also charged Dr. Vriesendorp with violating 21 C.F.R. § 312.50, but this provision applies to sponsors, rather than clinical investigators. Because Dr. Vriesendorp was not the sponsor of the study, he did not violate 21 C.F.R. § 312.50.
[53] A copy of Dr. Vriesendorp's signed Form FDA 1572 is Exhibit 1 to the CBER Reply.
[54] The regulation states in relevant part: An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations, for protecting the rights, safety and welfare of subjects under the investigator's care ...

the investigator to conduct the study in accordance with the current relevant protocol. A common element in all seven subcharges is that Dr. Vriesendorp deviated from the protocols for the IND [ ] studies.

Charge 2a – Protocol Violation, Patient Eligibility Criteria

The Center charged that Dr. Vriesendorp violated the regulation by deviating from the patient eligibility criteria of both protocols.[55] The Center contends that Dr. Vriesendorp admitted to the following deviations. (References to the Center's evidence of admissions, and protocols affected, are in the footnotes.)

Two subjects had platelet counts below the required cutoff.[56]

One subject had a Zubrod performance status above the required cutoff.[57]

One subject could not have passed the pulmonary function test.[58]

Two subjects had granulocyte counts below the required cutoff.[59]

Two subjects lacked the required life expectancy of greater than three months.[60]

CBER cites several bases for its contention that the violations were deliberate.[61] Dr. Vriesendorp is an experienced investigator,[62] and was author of the protocols.[63] Further, Dr. Vriesendorp knew how to change patient entry criteria by amending protocols, having previously requested a protocol change for a patient eligibility criterion.[64] In fact, he admitted that the protocols should have been amended to delete

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[55] CBER MSD, pp. 11-12.
[56] CBER MSD, Exhibit 2, p. 3, and Exhibit 5, pp. 2-3; protocols 92-001 and 95-004
[57] CBER MSD, Exhibit 2, p. 3; protocol was not referenced.
[58] CBER MSD, Exhibit 2, p. 4; protocol 92-001
[59] CBER MSD, Exhibit 2, p. 4; one subject under each protocol.
[60] CBER MSD, Exhibit 2, pp. 4-5; protocol was not referenced.
[61] Id., p. 17
[62] CBER Reply, pp. 4-5
[63] Technically, "Study Chairman." CBER MSD, Exhibit 26, Protocol 92-001
[64] CBER MSD, Exhibit 14 Dr. Vriesendorp's memorandum introducing, and Dr. [ ] memorandum distributing, amendments to Protocol [ ] regarding the patient age criterion.

the pulmonary function test.[65] Also, Dr. Vriesendorp knew that compassionate INDs (CINDs) could be used to treat subjects not meeting protocol eligibility criteria, having previously obtained CINDs.[66]

Finally, CBER argues that by signing the Form FDA-1572, Dr. Vriesendorp committed to follow relevant regulations, and agreed that he would not make changes except as provided in that form.[67] That form provides for, among other things, a commitment that the investigator will not make changes in the research without IRB approval, with limited exceptions not applicable to patients being considered for entry into the study.[68]

Dr. Vriesendorp makes both general and specific responses to the charges. He asserts the existence of several options for deviating from a protocol,[69] in addition to obtaining a CIND.[70] He places the greatest emphasis on what he claims to be a principal investigator's prerogative ("PI prerogative" or "PI override") to deviate from the protocol without prior approval from the IRB. He cites [ ] policy memos establishing a new protocol data management system to support his position that [ ] protocol policies offered flexibility to the principal investigator by allowing for an "override" in the best interest of the patient.[71] He also claims that an FDA letter to

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[65] CBER MSD, Exhibit 2, p. 3

[66] CBER MSD, Exhibit [ ] Investigator Study Manual, Compassionate IND Procedure; Exhibit 16, Vriesendorp requests for Compassionate INDs for three subjects.

[67] CBER MSD, p. 11

[68] The form includes a commitment that "... I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects." Obviously, the exception does not apply to persons who are not yet in the study, but are only seeking entry.

[69] Vriesendorp Opposition, p. 34. Vriesendorp argues that the deviations in this case were not violations. Id., p. 33

[70] Vriesendorp Opposition, p. 33

[71] Vriesendorp Opposition, Reference 4, is a January 8, 1996 memo to clinical faculty and others from [ ] MD, [ ] Associate Vice President for Clinical and Translational Research. The memo describes the mandatory implementation of the Protocol Data Management System (PDMS) for use in the registration of patients in clinical trials. Reference 5 is a March 15, 1996 memo from [ ] M.D., Associate Professor of Medicine, to

[ ] (the [ ] letter") "acknowledges the existence and legitimacy of the PI prerogative."[72] He further asserts that his deviations from protocol were always peer reviewed and documented.[73]

According to Dr. Vriesendorp, protocols and most FDA regulations are guidelines, not legal requirements.[74] He argues that patients with debilitating and life-threatening illnesses should be managed using a flexible approach.[75] He also asserts that the IND [ ] studies were flexible Phase 1 studies; therefore he could unilaterally make modifications not affecting critical safety assessments, reporting changes in the annual report.[76]

Dr. Vriesendorp responds to the Center's specific allegations as follows:

With regard to platelet and granulocyte count, he states that "hematological damage is not predicted by blood values such as platelet levels ... this observation invalidates the generic application of minimum hematological parameters as eligibility criteria."[77]

The patient with a low Zubrod score was accepted for compassionate reasons.[78]

[ ], MSD, discussing the requirement of completed checklists for deviation from protocol 92-001.

[72] Vriesendorp Opposition, p. 34, citing Vriesendorp Opposition Reference 62, January 9, 1997 letter from Boyd Fogle, FDA, to the president of [ ]

[73] Id., p. 33

[74] Id., p. 10

[75] Id.

[76] Vriesendorp Opposition, p. 9; Vriesendorp MSD, p. 2; Vriesendorp Reply, p. 6. Phase 1 studies are designed to determine the metabolism and pharmacological actions of the drug in humans, the side effects associated with increased doses and, if possible, to gain early evidence of effectiveness. Phase 2 studies are conducted to evaluate the effectiveness of the drug, and to determine short-term side effects and risks. Protocols for Phase 1 studies may be less detailed and more flexible that protocols for Phase 2 studies; modifications of the experimental design of Phase 1 studies that do not affect critical safety assessments are required to be reported to FDA only in the annual report. 21 C.F.R. §§ 312.21 and 312.23(a)(6).

[77] Vriesendorp Opposition, p. 36

[78] CBER MSD, Exhibit 2, p. 3.

Pulmonary function tests were performed only sporadically because they were expensive, unsafe and uninformative.[79] He had modified the protocol to exclude the tests in his studies at [ ], but forgot to change the protocol at [ ].[80]

The subjects with short life expectancy were treated in extremis, off protocol.[81]

Although Dr. Vriesendorp denies violating the regulation, he adds that there was too much confusion as to the proper procedure for deviating from the protocol for his actions to have constituted deliberate violations.[82]

Replying to Dr. Vriesendorp's general defense, the Center states that "it is never permissible for a clinical investigator to simply disregard the protocol requirements, which are designed to protect the safety of the subject and produce the most reliable results."[83] The Center points out that Dr. Vriesendorp, like all clinical investigators, must comply with FDA regulations, which are binding.[84] The clinical investigator regulations provide several options for protocol deviations,[85] primarily protocol changes that must be made through the IRB[86] and submitted to FDA as protocol amendments.[87]

With regard to the [ ] letter, the Center asserts that, instead of legitimizing a "PI override," the letter reflects the Center's concern that the [ ] new protocol data management system would not safeguard against clinical investigators' administering investigational new drugs, to patients who do not meet protocol criteria, without following proper procedures.[88] The Center references IND submissions

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[79] Vriesendorp Opposition, pp. 37-9
[80] CBER MSD, Exhibit 2, p. 3
[81] CBER MSD, Exhibit 2, p. 4
[82] Vriesendorp Opposition, p. 35
[83] CBER Reply, pp. 9-10
[84] Id., p. 4, Footnote 1
[85] Id., p. 9
[86] Id., pp. 8-9
[87] Id., p. 10
[88] Id., Footnote 2

(including one signed by Dr. Vriesendorp) that show that the studies were Phase 2 studies, not Phase 1 as Dr. Vriesendorp alleged.[89]

The Center asserts that Dr. Vriesendorp's scientific/medical arguments regarding specific allegations (e.g. platelet and granulocyte counts) are irrelevant; the IRB is the place to resolve these issues.[90]

Without question, Dr. Vriesendorp admits that he deviated from the patient entry criteria in the protocol, as alleged by the Center.[91] I agree with the Center that when he did so, Dr. Vriesendorp violated the regulation; 21 C.F.R. § 312.60 clearly obligated Dr. Vriesendorp to conduct the study according to the Form FDA 1572, which required the investigator to conduct the study in accordance with the current relevant protocol. The Center correctly states that scientific/medical issues related to the deviations needed to be addressed to the IRB. I agree with the Center that the studies were Phase 2, but even assuming (as Dr. Vriesendorp contends) that they were Phase 1, Dr. Vriesendorp's argument would be irrelevant. The latitude associated with Phase 1 studies relates to the design of the protocol. Once it is put in place, the protocol must be followed.[92]

Dr. Vriesendorp's assertion of a "PI override" privilege has no basis in the regulations. The [ ] policy memos[93] do not change the fact that Dr. Vriesendorp violated the clear requirements of the regulation and the signed Form FDA 1572. Even assuming the [ ] policy memos could have reasonably been read to mean that a PI "override" was in effect during the period in question, and that the "override" superseded the provisions of the regulation and the Form FDA 1572 (assumptions that I do not believe are supportable), Dr Vriesendorp's argument still fails. Dr. Vriesendorp did not

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[89] CBER Opposition, p. 4, citing Exhibit 1, Dr. Vriesendorp's original IND submission, and Exhibit 2, 1995 Protocol Amendment.
[90] CBER Reply, pp. 8-9
[91] Id., pp. 12-14
[92] 21 C.F.R. § 312.23(a)(6)(i) and (ii)
[93] Vriesendorp Opposition, References 4 and 5

offer evidence to support his claim that "deviations from protocol were always peer reviewed and documented."[94] The [ ] policy memos required documentation for departures from protocol. More significantly, [ ] itself concluded in its audit that the study's patient eligibility criteria deviations were far beyond permissible limits.[95] If Dr. Vriesendorp is to rely on an [ ] policy statement, then he must abide by [ ] interpretation of the statement.

The eight protocol violations establish that Dr. Vriesendorp violated the regulation repeatedly. I also conclude that Dr. Vriesendorp's explanations do not raise genuine issues of material fact with regard to deliberateness. His contention that confusion about the regulations' requirements precludes a finding of deliberateness is not well founded. Neither the regulation nor the commitment Dr. Vriesendorp made by signing the Form FDA 1572 contains any provision for the unilateral deviations that he made from the protocol, nor do they raise any legitimate confusion on this point. The conclusion that Dr Vriesendorp's actions were deliberate is supported further by his previous use of an appropriate process to amend a protocol, his authorship of the protocols, and his experience as an investigator.

I find that Dr. Vriesendorp has raised no genuine issues of material fact for hearing on Charge 2a. I conclude that Dr. Vriesendorp both repeatedly and deliberately violated 21 C.F.R. § 312.60 by enrolling patients in violation of the protocols' entry criteria, and therefore that CBER is entitled to judgment as a matter of law.

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[94] Vriesendorp Opposition, p. 33

[95] [ ] audits found, among other things, an 84 percent overall rate of failure to meet protocol [ ] eligibility criteria, a rate which far exceeded the accepted standard of less than five percent ineligibility. CBER MSD, Exhibits 8 and 9

Charge 2b – Protocol Violation, Platelet Level Stopping Criteria

The Center charged that Dr. Vriesendorp violated the stopping criteria in protocol [ ] by continuing to administer the test article to eight subjects when their blood platelet counts were below levels specified in the protocol. Platelet counts for all eight patients were less than half the protocol's minimum count, putting the patients at even greater risk of harm.[96] The Center contends that Dr. Vriesendorp admitted these violations.[97]

Dr. Vriesendorp's response is that the patients had low platelet counts because of the Hodgkin's disease and previous therapy, and needed the drug to treat the "real" cause of the low platelets, the underlying disease.[98]

Dr. Vriesendorp's actions and explanation were in direct disregard of the protocol. His argument is clearly one that he needed to take up with the IRB, and does not raise a genuine issue for a hearing. Dr. Vriesendorp's response indicates that he violated the protocol's stopping criterion willfully, and so I conclude not only that Dr. Vriesendorp violated the regulation, 21 C.F.R. § 312.60, but also that he did so deliberately. The eight violations establish that Dr. Vriesendorp violated the stopping criteria repeatedly.

I find that Dr. Vriesendorp has raised no genuine issues of material fact for hearing on Charge 2b. I conclude that Dr. Vriesendorp both repeatedly and deliberately violated 21 C.F.R. § 312.60 by violating the stopping criteria for protocol , and therefore that CBER is entitled to judgment as a matter of law.

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[96] CBER MSD, p. 13

[97] Id., citing CBER MSD Exhibit 2, p. 9. Dr. Vriesendorp attempts to justify the decision by stating that he and other physicians who were involved were experienced in the management of low platelet values, and decided that the risks of withholding therapy were greater than the risks of thrombopenia. Id.

[98] Vriesendorp Opposition, pp. 35-7

Charge 2c – Protocol Violation, Concurrent Therapy

The Center alleges that Dr. Vriesendorp deviated from both protocols by administration of concurrent therapies to five patients.[99] Specifically, the Center alleges that Dr. Vriesendorp admitted that three subjects received vincristine and two received external beam radiation ("radiation therapy") during treatment under the IND.[100] According to the Center, Dr. Vriesendorp intended the radiation to be an integral part of the treatment regimen. As an example, CBER included one patient's records showing that Dr. Vriesendorp administered the radiation therapy 53 days after administering the [ ] test article, and 16 days before administering a second course of the test article.[101]

Dr. Vriesendorp responds that vincristine and external beam radiation were not excluded by the protocol.[102] He states further that concurrent therapies were not mentioned in the protocols, and so he cannot be accused of violating the protocols.[103] According to Dr. Vriesendorp, other investigators use true concurrent therapy mixed therapies of chemotherapy, external beam radiation, and surgery. Dr. Vriesendorp considers his studies to be the best example of true single modalities.[104]

Dr. Vriesendorp admits administering vincristine to several patients[105] who "received vincristine at the end of their first radiolabeled antiferritin, more than 10 weeks after administration of [ ] Patients were evaluated for tumors before vincristine

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[99] CBER MSD, pp. 13-15

[100] Id., p. 14, citing CBER MSD Exhibit 2, p. 6

[101] Id., citing CBER MSD Exhibit 12. patient record and treatment notes showing treatment of one patient with the [ ] labeled article November 3, 1993, with the [ ] labeled article November 11, 1993, and external beam radiation treatment January 3-5, 1994, to be followed by completion of protocol treatment.

[102] Vriesendorp Opposition, pp. 29, 39-40

[103] Id., p. 39

[104] Id., p. 40, citing Vriesendorp Opposition Reference 71, Biodrugs article.

[105] Vriesendorp states that he administered vincristine to three patients in his Opposition, page 29 and to four patients in his Opposition at page 39. He also states that one of these patients had true concurrent therapy under a compassionate IND, Opposition at 39-40, but does not explain what that "true" concurrent therapy was.

administration." (Emphasis in original.)[106] He also admits to administering external beam radiation therapy to two patients, several days before initiation of protocol treatment.[107] He states that one of the two patients obtained stable disease, the other had almost complete recovery,[108] and that tumor response in areas treated by radiation was not evaluated. Therefore, according to Dr. Vriesendorp, tumor response and safety could be evaluated for all patients.[109]

The Center responds that Dr. Vriesendorp's claim that concurrent treatment somehow means only the treatment is administered simultaneously with the investigational treatment and that treatment with other therapies during the study period would not affect study results is without logic or merit.[110] The Center also argues that Dr. Vriesendorp did not establish that protocol treatment of the patients receiving vincristine had been completed before vincristine therapy was initiated.[111] The Center argues further that Dr. Vriesendorp's assertion that any treatment not mentioned in a protocol is permissible, if followed, would make study results uninterpretable.[112] The Center also calls attention to the fact that Dr. [ ] had informed Dr. Vriesendorp while Dr. Vriesendorp was still at [ ] that administration of external beam radiation

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[106] Vriesendorp Opposition, p. 40
[107] Id., p. 39
[108] Id.
[109] Id., p. 29
[110] CBER MSD, p. 14
[111] The Center states that Dr. Vriesendorp appears to suggest that because 10 weeks had elapsed since the [ ] administration, patients were no longer on protocol. The Center points out that after completion of a treatment cycle, another treatment cycle cannot begin until the patient's blood value recovers to predetermined levels. Because the recovery period will vary among patients, there is no standard recovery time; because Dr. Vriesendorp did not indicate which patients received vincristine 10 weeks after receiving the [ ] labeled product, a detailed response is impossible. Nor does he indicate whether vincristine was followed by another [ ] cycle. If additional cycles followed the vincristine, results of the treatment could be uninterpretable. CBER Reply, p. 15
[112] CBER Reply, pp. 14-15

prior to administration of [ ] would be a violation of the protocol for a similar study.[113]

It would not be reasonable to interpret the protocols' failure to prohibit concurrent therapy as meaning that any concurrent therapy is permitted. Such an interpretation could well render the study results unevaluable, and expose patients to unnecessary risk, all while following the protocol. I conclude that Dr. Vriesendorp's administration of vincristine and external beam radiation was concurrent therapy in violation of the protocol and the regulation. Vincristine was administered just before the second [ ] cycle; external beam radiation was administered just before the initial [ ] cycle. The administration of both concurrent therapies had the potential to expose patients to excessive treatment and to confound study results.

The violations were repeated because they involved more than one patient. They were also deliberate. Dr. Vriesendorp's argument that all treatments not excluded are permitted shows reckless disregard for the requirements that the study protocol be followed. In addition, he had specific warning from Dr. [ ] while at [ ] that a similar practice was not acceptable.

I find that there is no genuine issue of material fact for a hearing on Charge 2c. I conclude that Dr. Vriesendorp deliberately and repeatedly violated 21 C.F.R. § 312.60 by failing to follow the protocol by administering concurrent therapy not listed in the protocol, and therefore, that CBER is entitled to judgment as a matter of law.

Charge 2f – Protocol Violation, Safety Testing

The Center alleges that Dr. Vriesendorp deviated from protocol [ ] by failing to perform the required serum test for [ ] in any of his patients.[114] By

[113] Id., citing Vriesendorp Opposition Reference 7 (letter from Dr. [ ] to Dr. Vriesendorp)

doing so, the Center asserts, Dr. Vriesendorp exposed patients to potentially unnecessary radiation and put them at risk for allergic reactions.[115] The Center submitted evidence to establish that Dr. Vriesendorp admitted that the testing was not done.[116]

The Center urges a finding that Dr. Vriesendorp violated the regulation deliberately, based on Dr. Vriesendorp's admission that the tests were dropped in practice from the study.[117]

Dr. Vriesendorp explains that the tests were incorporated into the protocol because the study originally included an investigator who was interested in the [ ] tests.[118] However, Dr. Vriesendorp's experience at [ ] showed that the tests were unnecessary and did not contribute to patient safety. He states that [ ] formation in Hodgkin's patients was rare; adverse reactions and delayed symptoms did not occur. He also states that during the investigations, the [ ] [ ] [ ] scan proved to be a safe and sensitive *in vivo* method for determining the presence of [ ]. He did admit, however, that he was late in confirming his adjustment administratively.[119]

I agree with the Center that Dr. Vriesendorp violated the protocol by failing to perform the required [ ] test for [ ], and that his after the fact justification is inadequate to raise a factual issue for hearing.[120] If Dr. Vriesendorp had learned that the [ ] tests were unnecessary while he was still at [ ], he certainly could have sought concurrence from the IRB for his [ ] studies to use the

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[114] CBER MSD, p. 17. The test is specified in Section 5.11 of the protocol, CBER MSD Exhibit 26.
[115] Id.
[116] CBER MSD, Exhibit 2, p. 7, cited at CBER MSD p. 17.
[117] CBER MSD, pp. 19-20
[118] CBER MSD, Exhibit 2, p. 7
[119] Vriesendorp Opposition, pp. 41-3
[120] CBER Reply, p. 18

[ ] scans for determining the presence of anti-antibodies. Instead, he included the [ ] test in protocol [ ] but unilaterally decided not to use the test.

I find that Dr. Vriesendorp has raised no genuine issue of fact for hearing on Charge 2f. I conclude that Dr. Vriesendorp repeatedly and deliberately violated 21 C.F.R. § 312.60 by ignoring the protocol's specification of the serum test, and therefore that CBER is entitled to judgment as a matter of law.

B. Summary Decision Granted to Dr. Vriesendorp

Charge 2e – Protocol Violation, [ ] Imaging Study

The Center alleges that Dr. Vriesendorp deviated from section 5.4 of protocol [ ] by administering [ ] without an appropriate imaging study with [ ], thus exposing a patient to unnecessary risk caused by the presence of [ ].[121] This was the same patient whose treatment was the subject of Charge 1 (administration of [ ] without an IND). The Center notes that the patient did receive [ ], as documented by the patient's medical history.[122]

After first denying the allegation, Dr. Vriesendorp admitted that the imaging study had not been done with [ ], claiming it was done with a [ ] dose of [ ].[123]

Protocol [ ] is limited to the administration of [ ]. Although section 5.4 of the protocol does not specify [ ], it is clear that [ ] is contemplated. Dr. Vriesendorp administered [ ]

[121] CBER MSD, pp. 15-17
[122] CBER MSD, p. 16, citing Exhibit 13

[ ] to this patient, and so he cannot be said to have violated the protocol in this manner. Simply put, Dr. Vriesendorp could not have violated Protocol [ ] by failing to administer [ ], because the protocol called for administration of [ ].

I find that there are no genuine issues of material fact for a hearing on Charge 2e. I conclude that Dr. Vriesendorp did not violate 21 C.F.R. § 312.60 by administering [ ] to this patient, and therefore that Dr. Vriesendorp is entitled to judgment as a matter of law.

C. Genuine Issues of Material Fact for a Hearing

Charge 2d – Protocol Violation, Fractionated Dosing

The Center alleges that Dr. Vriesendorp deviated from protocol [ ] by administering fractionated (divided) doses of the [ ] to two patients. The protocol required a single dose.[124] The Center urges that this violation of the regulation was deliberate, because Dr. Vriesendorp admitted that a change to the protocol, to allow for the fractionated dose, was still under consideration by the IRB.[125]

Dr. Vriesendorp provided seemingly contradictory explanations for using the fractionated doses in the two patients: (1) tumors re-grew after the first undivided dose, and Dr. Vriesendorp wanted to retreat the patients earlier, with fewer side effects;[126] and (2) one patient had a complete response, and the other a partial response to the

[123] CBER MSD Exhibit 2, p. 7
[124] CBER MSD, p. 15
[125] CBER MSD, Exhibit 2, p. 6, Exhibit 5, pp. 3-4
[126] CBER MSD, Exhibit 2, p. 6

undivided doses, but both experienced bone marrow side effects.[127] He stated that the total of the two doses did not exceed the highest individual dose.[128]

Dr. Vriesendorp also stated that the new protocol ([ ]), which provided for a fractionated dose, had been reviewed by the IRB and essentially approved, but its formal approval had been delayed for administrative reasons. According to Dr. Vriesendorp, data from experience under the new protocol, after it was approved, appeared to confirm the original hypothesis that fractionation decreases side effects.[129]

Dr. Vriesendorp needed to adhere to the provisions of the protocol as long as they were in effect. In this case, however, the record is not clear as to whether Dr. Vriesendorp administered the fractionated doses before the effective date of the new protocol, which was several months earlier than the date of the memorandum formalizing the change.[130] The earlier effective date in the memorandum supports Dr. Vriesendorp's assertion that communication of the protocol's approval had been delayed for administrative reasons. Since there is inadequate information in the record for me to determine which of the two dates constitutes the actual date of approval of Protocol [ ], I find a genuine issue for hearing on Charge 2d. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 2d.

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[127] CBER MSD, Exhibit 5, p. 3
[128] Vriesendorp Opposition, pp. 40-1
[129] CBER MSD, Exhibit 2, p. 7
[130] CBER MSD, Exhibit 17, [ ] memo dated March 21, 1995, approving protocol [ ] with an official approval date of January 18, 1995. The record does not indicate when Dr. Vriesendorp administered the fractionated doses to the two patients that are subject of this charge.

Charge 2g – Dosimeter Calculations

The Center alleges that Dr. Vriesendorp deviated from both protocols for all patients by failing to perform dosimeter calculations,[131] and that Dr. Vriesendorp admitted the violation.[132]

Dr. Vriesendorp responds that current dosimeter methods are inaccurate, that he is working to improve the methods, and that the calculations were initiated, but are still pending. He argues that the calculations are not intended for prospective clinical decisions (i.e. there is no immediate effect on protocol design or patient management) but for retrospective correlation between observed tumor response and normal tissue damage.[133]

The Center responds that the protocol states that the calculations will be performed, and that Dr. Vriesendorp's claim that the calculations have been pending for years is spurious.[134] It does not, however, contend that the violation is deliberate.

The evidence before me on these motions does not establish a time by which the dosimeter calculations must be completed. Therefore, I find a genuine issue for a hearing on Charge 2g. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 2g.

Charge 3 – Failure to Report Deaths and Adverse Reactions

In this charge, the Center alleges violations of two sections, 21 C.F.R. §§ 56.103(a) and 312.66.

21 C.F.R. § 56.103(a) provides that a clinical investigation cannot be initiated unless it "has been reviewed and approved by, and remains reviewed and approved by, an IRB...."

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[131] CBER MSD, p. 17
[132] CBER MSD, Exhibit 2, p. 7
[133] Vriesendorp Opposition, pp. 43-4

21 C.F.R. § 312.66 requires an investigator to assure that an IRB will be responsible for initial and continuing review and approval of the study, and to promptly report to the IRB all changes in research activity and unanticipated problems involving risk to humans. This section also prohibits the investigator from making changes in the research without IRB approval, except to eliminate immediate hazards to the subjects.

The Center makes two subcharges, as described below.

Charge 3a – Failure to Report Patient Deaths to the IRB

The Center charges Dr. Vriesendorp with failure to report promptly to the IRB the deaths of two subjects in 1995, dying 18 days and 49 days after administration of the investigational drug.[135] According to CBER, the IRB approval letter informed Dr. Vriesendorp that he was to promptly report the death of any patient in the study to the Surveillance Committee.[136] The Center asserts that Dr. Vriesendorp admitted not reporting the deaths,[137] and that the violation was deliberate.[138]

Dr. Vriesendorp responded by, among other things, stating that the deaths were not caused by the investigational drug,[139] that 21 C.F.R. § 312.32(c)(1)(A) requires reporting only adverse reactions that are both serious and unexpected, and that he was not made aware of the new reporting requirements until April 1996.[140]

Dr. Vriesendorp's claim of ignorance does not raise a genuine issue for hearing, especially since the [ ] memo requiring reporting of all deaths was addressed to him. I find that he failed to respond to this memo, and I emphasize that it is extremely important that deaths be reported.

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[134] CBER Reply, pp. 18-19, CBER MSD, Exhibit 26
[135] CBER MSD, p. 20
[136] CBER MSD, Exhibit 17 [ ] memo dated March 21, 1995, approving protocol [ ].
[137] CBER MSD, Exhibit 5, pp. 4-5
[138] CBER MSD, pp. 22-23
[139] CBER MSD, Exhibit 2, p. 9

However, the question presented here is whether Dr. Vriesendorp's failure violated any regulations. The most specific requirement in the regulations the Center relies on (21 C.F.R. § 312.66) requires the reporting of "unanticipated problems." However, the Center presented no evidence to establish that the deaths were unanticipated.

Summary decision cannot rest on mere allegations. Neither CBER nor Dr. Vriesendorp has presented any evidence as to whether these deaths were unanticipated. Therefore, I conclude that there are genuine issues of material fact for hearing on Charge 3a. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 3a.

Charge 3b – Failure to Report Adverse Reactions to the IRB

The Center alleges that Dr. Vriesendorp failed to report to the IRB two patients' severe adverse reactions.[141] One patient had grade 4 thrombocytopenia; the other complete bone marrow aplasia, fever and subsequent fungal sepsis. The Center again relies on the IRB approval letter, asserting that Dr. Vriesendorp was required by the [ ] to report any severe adverse effects.[142] (In its opposition to Dr. Vriesendorp's Motion for Summary Decision, the Center added that Dr. Vriesendorp was required by 21 C.F.R. § 312.64(b) to report adverse reactions caused by, or probably caused by, the drug.[143]) The Center asserts that the failure to report these reactions was deliberate.[144]

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[140] Vriesendorp Opposition, pp. 45-6
[141] CBER MSD, pp. 21- 22
[142] CBER MSD, exhibit 17, March 21, 1995 [ ] memo.
[143] CBER Opposition, p. 8
[144] CBER MSD, pp. 23-4

Dr. Vriesendorp's response, though intermingled with that for patient deaths[145] and somewhat confusing,[146] is essentially the same as for Charge 3a, above, that is, that there is no requirement that these particular adverse events be reported.

My decision here is the same as for Charge 3a. Again, I want to emphasize the importance of reporting adverse reactions, as required by the regulations. However, the question presented here is whether Dr. Vriesendorp's failure to report the adverse reactions to the IRB violated any regulation, when the regulation requires the reporting only of unanticipated problems. Neither the Center nor Dr. Vriesendorp presented evidence to establish that the adverse events were, or were not, unanticipated.

I would add that the Center's reliance on 21 C.F.R. § 312.64(b) provides inadequate notice to Dr. Vriesendorp because this regulation was not cited in the NOOH or in CBER's Motion for Summary Decision.[147] Even if the notice was adequate, the Center did not meet its burden of establishing that the adverse event was caused by, or probably caused by the therapy. CBER presented no evidence of a temporal association between the adverse event and administration of the drug. Moreover, 21 C.F.R. § 312.64(b) requires that adverse events be reported to the sponsor, not the IRB. In this case, the [ ] was the sponsor of the study, but CBER presented no evidence whatsoever about the reporting of the adverse events to the sponsor.

Summary decision cannot rest on mere allegations. Neither CBER nor Dr. Vriesendorp presented any evidence as to whether these adverse events were unanticipated, or probably caused by the investigational drug. Therefore, I conclude that there are genuine issues of material fact for a hearing on Charge 3b. However, because

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[145] Vriesendorp Opposition, pp. 45-6

[146] Id., pp. 27-9

[147] As noted in the text, the Center cited the regulation for the first time in its Opposition to the Vriesendorp MSD.

my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 3b.

Charge 4 -- Failure to Maintain Adequate Records

The Center alleged violation of 21 C.F.R. §§ 312.60 and 312.62(a), which require the investigator to maintain adequate and accurate records of the disposition of the investigational drugs. The charge pertains to the adequacy of records related to the [ ] test article, quality control testing and prescriptions, additional manufacturing procedures and test article inventories.[148]

This charge is not well documented and supported, e.g. the Center did not submit investigator affidavits or otherwise explain the regulations' requirements and how those requirements were not met. Dr. Vriesendorp's Opposition was rather unresponsive to the Center's brief.[149]

Therefore, I find there are genuine issues of material fact for a hearing on Charge 4. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 4.

Charge 5 – Failure to Submit Adverse Reactions to Sponsor

21 C.F.R. § 312.64(b) requires an investigator to report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. The Center alleged violation of that regulation by Dr. Vriesendorp's failure to report promptly to the [ ] the adverse effects observed in two patients.[150]

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[148] CBER MSD, pp. 24-6

[149] Vriesendorp Opposition, pp. 47-8 For example, Dr. Vriesendorp defers without explanation or elaboration to documents submitted with his Request for Hearing.

[150] CBER MSD, pp. 27-9. These are different patients than those cited in Subcharge 3b.

Dr. Vriesendorp claims that the adverse reaction in one patient (chills and fever in association with administration of a [ ] dose of the drug) apparently was due to a small amount of [ ] present in [ ][151] The Center responds that Dr. Vriesendorp lacked the test data to exclude allergic reactions as the cause[152] but does not provide evidence to support its claim or otherwise elaborate. Therefore, Dr. Vriesendorp has raised a genuine issue of material fact with respect to whether the adverse effect may reasonably be regarded as being caused by, or probably caused by, the investigational drug.

The record with respect to the adverse effect on the other patient is not clear. The Center states that the patient experienced hard chills and fever during administration of the [ ] product[153] but the reference it cites does not make such a statement.[154] Another reference refers to headaches and other symptoms.[155] Further, the Center did not present evidence that would establish a temporal association between the administration of the drug and any adverse reaction. Therefore, Dr. Vriesendorp also raised a genuine issue of material fact with respect to whether the investigational drug caused or probably caused an adverse reaction in this patient.

Accordingly, I find that there are genuine issues of material fact for hearing on Charge 5. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 5.

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[151] CBER MSD, Exhibit 2, p. 12
[152] CBER MSD, p. 28
[153] Id
[154] CBER MSD, Exhibit 2, p. 11
[155] CBER MSD, Exhibit 23

Charge 6 -- Lack of Informed Consent

21 C.F.R. § 312.60 requires investigators to obtain informed consent in accordance with the provisions of Part 50. 21 C.F.R. Part 50 contains information about the general requirements and the elements of informed consent, exceptions from general requirements, and the ways of documenting informed consent. The Center alleges two violations of this section.

Charge 6a – Informed Consent, Low Blood Cell Counts

The Center alleges that one statement in the study's consent form implies that the study would not cause long-term low blood cell counts ("blood counts will return to pretreatment levels but might require additional measures").[156] The Center asserts that this statement does not accurately reflect the actual hematological profile following administration of the test article. However, the Center concedes that the wording might have been acceptable if Dr. Vriesendorp had not enrolled study subjects who did not meet protocol eligibility requirement.

Dr. Vriesendorp responds that he did not expect that lower blood counts would predict for more serious side effects.[157] He states that it is not uncommon for Hodgkin's Disease patients to become "hematological cripples" by prior therapy. Such patients respond to [ ] treatments with serious and prolonged blood count depressions, but cannot be identified by measuring blood counts prior to study entry.

I have already concluded that Dr. Vriesendorp violated the protocol and 21 C.F.R. § 312.60 by enrolling subjects whose platelet levels were lower than permitted by the protocol. However, Dr. Vriesendorp has raised the issue whether these patients would be likely to experience long-term low blood cell counts. Therefore, I conclude that

[156] CBER MSD, p. 30, citing Exhibit 24, p. 2
[157] Vriesendorp Opposition, pp. 49-50

there remains a question whether the informed consent was inadequate for patients who did not meet platelet level entry criteria.

Accordingly, I find that there are genuine issues of material fact for a hearing on Charge 6a. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 6a.

Charge 6b – Informed Consent, Safety Testing

The Center alleges that the consent form states that patients will be removed from the study if they develop [ ] against the injected [ ].[158] Because the protocol states that patients' serum will be tested for [ ],[159] and because Dr. Vriesendorp did not perform the serological testing for developing [ ] [ ] as described above (Charge 2f), the Center contends that the consent form was misleading because it incorrectly implies that the investigator would monitor development of [ ].

Dr. Vriesendorp responds that he did test for [ ], by conducting the [ ] scan. He asserts that [ ] tests were not described or promised in the consent form, and that [ ] tests were found to be a good replacement for the serum tests.[160]

In its Reply, CBER argues that the [ ] scan could not be used as testing for [ ] because the consent form says that [ ] testing will be conducted before any [ ] is injected.[161] However, this sequence of events is not supported by the protocol. According to protocol section 5.1, [ ]

[158] CBER MSD, pp. 31-2. Citing Exhibit 25, Consent Form
[159] CBER MSD, Exhibit 26, Section 5.11
[160] Vriesendorp Opposition, p. 50
[161] CBER Reply, p. 24.

[ ] is to be administered on day one.[162] Protocol section 5.11 states that patients' serum will be tested for [ ] after day 7 and 14.[163]

I conclude that the informed consent form does state that allergic testing will be conducted, but does not specify or imply that it will be conducted by serological testing. I also conclude that there remains a question whether the [ ] scans were an appropriate way to conduct allergy testing.

Therefore, I find that genuine issues of material fact remain for a hearing on whether Dr. Vriesendorp conducted the allergy testing contemplated by the informed consent form. However, because my findings on other charges are sufficient to warrant a recommendation of disqualification, a hearing need not be held on Charge 6b.

D. Additional Argument by Dr. Vriesendorp

Dr. Vriesendorp complains that the sponsor did not educate him in the rules with regard to clinical investigations, as required by the regulation,[164] and therefore any violations were not deliberate. In fact, he claims that he was not even aware of the existence of the C.F.R. until April 1996.[165] He also complains that [ ] did not appoint a separate monitor for the studies, instead designating him (Dr. Vriesendorp) as his own monitor.[166]

Dr. Vriesendorp's defenses are not well founded. Although the sponsor does have educational responsibilities, Dr. Vriesendorp, as the investigator, is responsible for knowing and complying with the regulations. Form FDA 1571 (IND submissions) and Form FDA 1572 (Investigator Statement), both of which Dr. Vriesendorp signed, contain

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[162] CBER MSD. Exhibit 26. See also protocol section 5.3 requiring serial planar whole body gamma camera scans on days 1, 2, and 3, that is, after administration of [ ].

[163] Id.

[164] Vriesendorp Opposition, p. 17

[165] Id., p. 57

references to the applicable sections of the C.F.R. The FDA's initial IND acknowledgement letter, written to Dr. Vriesendorp as the purported sponsor, enclosed a copy of 21 C.F.R. Part 312.[167] As for the lack of a separate study monitor, Dr. Vriesendorp named himself as monitor (in addition to sponsor and investigator) in his first submission to FDA.[168] In addition, he does not assert that he asked [ ] at any time to appoint a separate monitor.

For these reasons, Dr. Vriesendorp's assertions do not prevent a finding of deliberateness where the other evidence supports such a finding.

VI. CONCLUSIONS

After reviewing the charges and evidence presented by both parties, I find that Dr. Vriesendorp violated the regulations as follows:

With respect to Charge 1, I find that he violated 21 C.F.R. §§ 312.20 and 312.40(d) when he administered [ ] in place of [ ] [ ] without having an IND for use of the [ ] product.

With respect to Charge 2, I find that he violated 21 C.F.R. § 312.60, by deviating from the protocols for IND [ ] in the following ways:

Charge 2a – Patient Eligibility Criteria

Charge 2b – Platelet Level Stopping Criteria

Charge 2c – Concurrent Therapy, and

Charge 2f – Safety Testing.

In deviating from the protocol in these ways, Dr. Vriesendorp failed to fulfill the general responsibilities of an investigator as required by 21 C.F.R. § 312.60.

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[166] Id., p. 17
[167] Id., Reference 26

Dr. Vriesendorp has raised no genuine and substantial issues of fact with regard to these charges; therefore I grant summary decision to the Center on Charge 1 and Charges 2a, 2b, 2c, and 2f. I further find, as a matter of law, that Dr. Vriesendorp violated regulations 21 C.F.R. §§ 312.20 and 312.40(d) (Charge 1) deliberately, and violated regulation 21 C.F.R. § 312.60 (Charge 2a, 2b, 2c, and 2f) repeatedly and deliberately.

I find that Dr. Vriesendorp did not violate 21 C.F.R. § 312.60 by failing to conduct a [ ] imaging study. CBER has raised no genuine issues of material fact requiring a hearing on this charge. Therefore, I grant summary decision to Dr. Vriesendorp on charge 2e.

I find that genuine issues of material fact remain on the following charges:

Charge 2d – Protocol Violation, Fractionated Dosing

Charge 2g – Protocol Violation, Dosimeter Calculations

Charge 3a – Failure to Report Patient Deaths

Charge 3b – Failure to Report Adverse Reactions

Charge 4 – Failure to Keep Adequate Records

Charge 5 – Failure to Make Required Safety Reports

Charge 6a – Informed Consent, Low Blood Cell Counts, and

Charge 6b – Informed Consent, Safety Testing.

Because my findings as to Charges 1 and 2a, 2b, 2c, and 2f are sufficient to warrant a recommendation under 21 C.F.R. § 312.70 to disqualify Dr. Vriesendorp, a hearing is not needed on any of the issues for which a genuine issue of material fact remains.

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[168] CBER Opposition, Exhibit 1

VII. RECOMMENDATION

FDA's two major goals in enforcing the Clinical Investigator regulations are to ensure that investigators conduct accurate and reliable scientific studies, and to provide for patient protection. Adherence to a properly approved study protocol is absolutely essential to achieving these goals. I agree with the Center that "[a] study protocol incorporates measures designed to protect the safety of subjects receiving an experimental drug, as well as preserve the validity of the study; the IRB approves the protocol based on the investigator's assurances that these measures will be observed."[169] By deviating from the approved protocols, Dr. Vriesendorp substituted his judgment for that of the scientific community as represented by the IRB. If investigators had the unrestrained prerogative to depart unilaterally from their studies' protocols, as Dr. Vriesendorp asserts, the integrity of the clinical investigator system would be fatally compromised and patients' health would be routinely put at risk.

The risk to patient health from Dr. Vriesendorp's protocol violations can hardly be overstated. For example, his deviations from the protocols' platelet and granulocyte count criteria for enrolling patients in the study raise serious safety issues because administration of the drug to patients with low counts could result in the patients' bleeding to death.

Based on my findings of repeated and deliberate violations of the regulations, I recommend that the Commissioner disqualify Huibert M. Vriesendorp, M.D. from being eligible to receive investigational new drugs.

John J. McCormick, M.D.
Presiding Officer

Date: 11/17/00

[169] CBER Reply, p. 8

Exhibit 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

October 18, 1999

In reply refer to file F99-9693

Dr. Hulbert Vriesendorp
[ ];

Dear Dr. Vriesendorp:

This is in reply to the April 9, 1999 request submitted by [ ] on your behalf, for material regarding various documents. This request was received in the Center for Biologics Evaluation and Research on April 28, 1999. Based on Mr [ ] letters dated April 29, 1999 and May 4, 1999, this response has been provided directly to you.

Enclosed are the documents you have requested. In accordance with our telephone conversation we are not providing duplicates of those documents already released to you by Mr. Cohen, or those documents signed by you, as you requested. Please note that where such documents existed in the enclosed material, you will find pages marked "THIS PAGE WAS DETERMINED TO BE NOT RESPONSIVE TO YOUR REQUEST".

In order to help reduce processing time and costs, certain other material has been deleted from the records furnished to you, because a preliminary review of the records indicated that the deleted material is not required to be publicly disclosed. Such material has been marked "THIS PAGE WAS DETERMINED TO BE NOT RELEASABLE". If, however, you desire to review the deleted material, please make an additional request to the following address:

Food and Drug Administration
Freedom of Information Staff, HFI-35
5600 Fishers Lane
Rockville, MD 20857

Should the Agency then deny this information, you would have the right to appeal any such denial. Any letter of denial will explain how to make this appeal.

The following will be included in a monthly invoice:

Reproduction	1229	Pages	$122.90
Search	½	Hours	$14.50
Total			$137.40

The above charges may not reflect final charges for this request. Please DO NOT send any payment until you receive an invoice from the Agency's Freedom of Information Staff (HFI-35).

If we can be of further assistance, please let us know by referencing the above file number.

Sincerely yours,

Jamie Natour, Consumer Safety Officer
Access Litigation & Freedom of Information Branch (HFM-48)
Division of Disclosure & Oversight Management
Office of Communication, Training and Manufacturers Assistance
Center for Biologics Evaluation and Research
Food and Drug Administration

Enclosures

Exhibit 2

HMVriesendorp, MD, PhD
[ ]

Jamie Natour, Consumer Safety Officer
Access Litigation & Freedom of Information Branch (HFM-48)
Division of Disclosure & Oversight Management
Office of Communication, Training and Manufacturers Assistance
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

November 9, 1999

Re: File [ ]

Dear Consumer Safety Officer Natour,

I hope you do not mind being addressed in a shortened version of your lengthy and scary job description. I am in receipt of the 1229 pages of documents you sent to me in response of my FOIA's of 1996, 1997 and 1999. You considered 115 pages as "not responsive to my request", because they were already in my possession or addressed to me or signed by me. The same appears to hold for the documents that you did send. Ninety five percent of all documents were already in my possession for the reasons indicated above. The remaining 5 % is new, but uninformative as they represented copies of bills sent to patients. An additional 255 (two hundred fifty five) pages were considered "not releasable" for reasons unknown to me.

Following your kind suggestion I now do request to review the deleted material by means of copying this letter to FDA, Freedom of Information Staff HFI-35, 5600 Fishers Lane, Rockville MD 20857. I enclose a copy of my recent letter to DR Linda Ann Sherman, MD, Presiding Officer of the Disqualification Hearing, for your information.

I hope you understand my serious disappointment in the functioning of the FOIA process and request your assistance in resolving the remaining issues in a fair, open and expeditious manner.

Sincerely

HM Vriesendorp, MD PhD
CC Linda Ann Sherman, MD
Steve H Unger, Acting Chief Mediator and Ombudsman
FDA FOIA Staff