

Regulatory Information

DHHS-FDA Regulatory Hearing on the Proposal to Disqualify Huibert M. Vriesendorp, M.D. from Receiving Investigational New Drugs-Commissioner's Decision



Department of Health and Human Services

Food and Drug
Administration
Rockville, MD 20857

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I have reviewed the record of the regulatory hearing involved Huibert M. Vriesendorp, M.D., the summary decision of the Presiding Officer, the parties' summary decision memoranda with attachments, and the parties' submissions requesting review of the summary decision. Based upon my review, I have concluded that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR Parts 56 and 312 in connection with an investigational new drug study of **[redacted]**. Consistent with 21 CFR § 312.70(b), I have determined that Dr. Vriesendorp is no longer entitled to receive investigational drugs. The reasons for my decision are

set forth in the enclosed.

Dr. Vriesendorp may seek to have his eligibility to receive investigational drugs reinstated pursuant to 21 CFR 312.70(f) upon presentation of adequate assurances that the investigator will employ investigational drugs solely in compliance with the provisions of 21 CFR Parts 50, 56, and 312.

Sincerely,

/s/

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy
Commissioner

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY

HUIBERT M. VRIESENDORP, M.D.

FROM RECEIVING INVESTIGATIONAL NEW DRUGS

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 CFR § 312.70 and 21 CFR Part 16, whether Huibert M. Vriesendorp, M.D., a clinical investigator, should be disqualified from receiving investigational new drugs. John J. McCormick, M.D., serves as the presiding officer for this disqualification. Dr. McCormick issued a summary decision in favor of the Center for Biologics Evaluation and Research (CBER) and recommends that Dr. Vriesendorp be disqualified.

Based upon my review of the administrative record in this matter, including Dr. McCormick's summary decision and the parties' submissions, I conclude that Dr. Vriesendorp repeatedly and deliberately violated the regulations governing clinical investigations. Therefore, I am disqualifying Dr. Vriesendorp from receiving investigational drugs. The reasons for my decision follow.

I. PROCEDURAL BACKGROUND

The charges in this proceeding arose out of the investigation of Dr. Vriesendorp's use of **[redacted]** in the treatment of subjects with Hodgkins disease, a form of cancer. While at the University of **[redacted]** (**[redacted]**), Dr. Vriesendorp received authorization under IND **[redacted]** to begin studies of the **[redacted]** in accordance with study protocol **[redacted]**. Dr. Vriesendorp was listed as the principal investigator and the **[redacted]** (through **[redacted]** M.D.) was listed as the sponsor. The Institutional Review Board (IRB) for the study was the **[redacted]** Surveillance Committee, Office of Protocol Research. The study began in late 1992. On March 21, 1995, the **[redacted]** IRB approved revised protocol **[redacted]** written by Dr. Vriesendorp for a new study under IND **[redacted]**. Dr. Vriesendorp was listed as the principal investigator and the **[redacted]** (through **[redacted]** M.D.) was listed as the sponsor. The IRB remained the same. According to Dr. Vriesendorp, more than 100 subjects received treatment under IND **[redacted]** between October 1992 and December 1995. Dr. Vriesendorp's Opposition to CBER's Motion for Summary Decision at 17. The Food and Drug Administration (FDA) placed a clinical hold on IND **[redacted]** in October 1995 and conducted an audit of the studies under IND **[redacted]** in April 1996.

In a letter dated September 19, 1997, FDA's Associate Commissioner for Regulatory Affairs informed Dr. Vriesendorp that he would be given an opportunity for a regulatory hearing under 21 CFR Part 16 to determine whether he should be

disqualified from receiving investigational drugs. The notice of opportunity for a hearing (NOOH) was issued pursuant to 21 CFR §§ 312.70 and 16.22. The NOOH alleged violations of 21 CFR Parts 50, 56, and 312. Dr. Vriesendorp requested a hearing in a letter dated October 24, 1997. On May 14, 1999, CBER moved for summary decision on fourteen charges:

1) Charge 1: failure to submit an IND to FDA and failure to withhold administration of an investigational new drug until an IND was in effect, specifically administration of **[redacted]** (for which Dr. Vriesendorp did not have an IND in effect) in place of **[redacted]** (for which Dr. Vriesendorp did have IND **[redacted]** in effect), in violation of 21 CFR §§ 312.20, 312.40(d), and 312.50;

2) Charge 2a: failure to fulfill the general responsibilities of an investigator by providing investigational new drugs to subjects who did not meet the protocol eligibility criteria, in violation of 21 CFR § 312.60;

3) Charge 2b: failure to fulfill the general responsibilities of an investigator by administering investigational new drugs to subjects below protocol-specified blood platelet levels, in violation of 21 CFR § 312.60;

4) Charge 2c: failure to fulfill the general responsibilities of an investigator by administering two concurrent therapies not specified in the protocols, in violation of 21 CFR § 312.60;

5) Charge 2d: failure to fulfill the general responsibilities of an investigator by administering a fractionated (divided) dose of an investigational new drug in contradiction of the protocol's requirements, in violation of 21 CFR § 312.60;

6) Charge 2e: failure to fulfill the general responsibilities of an investigator by deviating from the protocol by administering a **[redacted]** without an appropriate imaging study with a **[redacted]**, in violation of 21 CFR § 312.60;

7) Charge 2f: failure to fulfill the general responsibilities of an investigator by deviating from the protocol by failing to perform a required serum test for **[redacted]**, in violation of 21 CFR § 312.60;

8) Charge 2g: failure to fulfill the general responsibilities of an investigator by deviating from the protocols by failing to perform dosimeter calculations, in violation of 21 CFR § 312.60;

9) Charge 3a: failure to ensure initial and continuing review and

approval by an Institutional Review Board (IRB) by failing to report certain deaths, in violation of 21 CFR §§ 56.103(a) and 312.66;

10) Charge 3b: failure to ensure initial and continuing review and approval by an IRB by failing to report certain adverse reactions, in violation of 21 CFR §§ 56.103(a) and 312.66;

11) Charge 4: failure to maintain adequate and accurate records relating to the investigational new drugs, in violation of 21 CFR §§ 312.60, 312.62;

12) Charge 5: failure to prepare and submit investigator reports by failing to report certain adverse reactions to the sponsor, in violation of 21 CFR § 312.64;

13) Charge 6a: failure to obtain informed consent because of misleading statements in the consent form regarding low blood cell counts, in violation of 21 CFR Part 50 and 21 CFR § 312.60; and

14) Charge 6b: failure to obtain informed consent because of misleading statements in the consent form regarding safety testing to detect the development of **[redacted]**, in violation of 21 CFR Part 50 and 21 CFR § 312.60.

Under 21 CFR § 16.26(b), the presiding officer may issue a summary decision on any issue when there is no genuine and substantial issue of fact respecting that issue. Based upon the evidence presented in and attached to CBER's summary decision motion, Dr. Vriesendorp's opposition to CBER's motion, CBER's reply to Dr. Vriesendorp's opposition, Dr. Vriesendorp's summary decision motion, CBER's opposition to Dr. Vriesendorp's motion, and Dr. Vriesendorp's reply to CBER's opposition, Dr. McCormick issued a summary decision on five of the charges in favor of CBER on November 17, 2000.

Dr. McCormick found that there were no genuine and substantial issues of fact with regard to Charges 1 and 2a, 2b, 2c, and 2f and issued summary decision in favor of CBER on those charges. Dr. McCormick found that there were no genuine and substantial issues of fact with regard to Charge 2e and issued summary decision in favor of Dr. Vriesendorp on that charge. Finally, on Charges 2d, 2g, 3a, 3b, 4, 5, 6a, and 6b, Dr. McCormick found that a determination could not be made without further evidence, and therefore denied CBER's motion for summary decision on those charges. Based upon these findings, Dr. McCormick recommended that I disqualify Dr. Vriesendorp.

On January 11, 2001, Dr. Vriesendorp requested that I review the summary decision and not concur in Dr. McCormick's recommendation. In addition to

disputing Dr. McCormick's factual findings on the five charges he determined that Dr. Vriesendorp violated, Dr. Vriesendorp requested review of the summary decision arguing that (1) Dr. McCormick applied the incorrect standard of proof, (2) Dr. McCormick ignored inferences favoring Dr. Vriesendorp, (3) Dr. McCormick gave the term "deliberately" a meaning that is inconsistent with its common legal meaning, (4) Dr. Vriesendorp did not receive all the information he asked for in a Freedom of Information Act (FOIA) request related to FDA's 1996 investigation of IND **[redacted]**, and (5) that the violations Dr. Vriesendorp was charged with violating were not material to warrant disqualification. Also on January 11, 2001, CBER requested that I review four of Dr. McCormick's recommendations. In response, Dr. Vriesendorp submitted a response, dated January 19, 2001, to CBER's request for Commissioner review. Finally, CBER submitted a response to Dr. Vriesendorp's response, dated February 12, 2001.

II. DECISION

In order to conclude that a clinical investigator is no longer eligible to receive investigational drugs, I must find that the investigator repeatedly or deliberately violated FDA regulations, or repeatedly or deliberately submitted false information to FDA or to the sponsor. Section 312.70(b) of Title 21 of the Code of Federal Regulations provides, in relevant part, that:

[a]fter 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 50, or Part 56, 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.

Therefore, a determination that an investigator either repeatedly or deliberately failed to comply with the regulations or submitted false information is a sufficient basis for disqualification.

In this proceeding, Dr. Vriesendorp is charged with repeatedly or deliberately failing to comply with 21 CFR Parts 50, 56, and 312. I will, as Dr. McCormick did in his summary decision, separately address each of the charges briefed in the parties' summary decision memoranda.

A. Factual Disputes on Five Charges that the Presiding Officer Granted Summary Judgment for CBER and that are Contested by Dr. Vriesendorp

Charge 1: Administration of [redacted] Without an IND

CBER charged that Dr. Vriesendorp administered **[redacted]** under IND **[redacted]** to subject 153743 on October 14, 1993, without having an IND in effect permitting the use of this investigational drug, in violation of 21 CFR §§ 312.20, 312.40(d), and 312.50. The protocol for IND **[redacted]** (which Dr. Vriesendorp authored) allowed for the use of **[redacted]** on enrolled subjects. CBER alleged that by failing to submit an IND to FDA for use of the **[redacted]** and by failing to withhold administration of the **[redacted]** until such an IND was in effect, Dr. Vriesendorp deliberately violated the regulations cited above .

In response, Dr. Vriesendorp admitted that he administered the **[redacted]** and that he lacked the authority to do so under IND **[redacted]**. However, Dr. Vriesendorp asserted that this action was not a deliberate violation since he was under an erroneous assumption that he could still use the **[redacted]** under IND **[redacted]**. That IND, for which Dr. **[redacted]** of **[redacted]** was the sponsor, covered the use of **[redacted]**. Dr. Vriesendorp worked under Dr. **[redacted]** as an investigator under IND **[redacted]**. Dr. Vriesendorp claimed that he never received notice from Dr. **[redacted]** that he had been removed from IND **[redacted]** as an investigator in 1990. [\[1\]](#)

Dr. Vriesendorp relied on two letters to support his position. The first, dated September 5, 1990, is from **[redacted]**, PhD, at **[redacted]** (**[redacted]** letter), to Dr. **[redacted]**, at the University of **[redacted]** (**[redacted]**). In this letter, Dr. **[redacted]** states that he was looking forward to continued collaboration with Dr. **[redacted]**, that he would send **[redacted]**, and that he would send additional **[redacted]** as needed. The second letter, dated April 19, 1996, is from **[redacted]**, at **[redacted]** (**[redacted]** letter), to FDA. In this letter, Dr. **[redacted]** states that he had no record or memory of shipment of **[redacted]** to Dr. Vriesendorp at **[redacted]** (**[redacted]**). Dr. Vriesendorp argued that this letter supported his position that Dr. **[redacted]** did not destroy **[redacted]** stocks or inform investigators that IND **[redacted]** and its investigational **[redacted]** were no longer available for study. Dr. Vriesendorp asserted that Dr. **[redacted]**, who had worked under IND **[redacted]** and IND **[redacted]** (another IND for **[redacted]**) while at **[redacted]**, brought the **[redacted]** to **[redacted]** from **[redacted]**. Thus, Dr. Vriesendorp asserted that he could reasonably believe that Dr. **[redacted]** had received the **[redacted]** under an IND that was still effective. Dr. Vriesendorp's request for Commissioner Review at 11.

In his Summary Decision, Dr. McCormick found that there were no genuine issues of fact for a hearing on Charge 1 and that Dr. Vriesendorp deliberately violated 21 CFR §§ 312.20 and 312.40(d). Dr. McCormick found that the **[redacted]** and **[redacted]** letters did not refer to IND **[redacted]** or provide any evidence that

Dr. Vriesendorp was authorized or believed himself authorized to administer the **[redacted]** in 1993 under IND **[redacted]**. Further, Dr. McCormick examined the record and found that Dr. Vriesendorp's conflicting explanations (discussed in detail below) as to the source of the **[redacted]** undermined the credibility of Dr. Vriesendorp's argument. Finally, Dr. McCormick found that Dr. Vriesendorp's failure to ascertain whether administration of **[redacted]** was covered by any active IND at a minimum demonstrated a reckless disregard for Part 312's requirements. Thus, Dr. McCormick issued a summary decision in favor of CBER on this charge.

After reviewing the administrative record, I affirm Dr. McCormick's findings for Charge 1 under 21 CFR § 312.40(d).^[2] The record is clear that Dr. **[redacted]** notified FDA that Dr. Vriesendorp was removed as an investigator under IND **[redacted]**, that Dr. Vriesendorp left **[redacted]** in 1990, and that Dr. **[redacted]**, as the sponsor for IND **[redacted]**, never authorized the use of the **[redacted]** at **[redacted]**. Dr. Vriesendorp failed to submit any evidence that showed he believed he was working under IND **[redacted]** or IND **[redacted]** while conducting studies under IND **[redacted]**, which he authored. Dr. Vriesendorp was unable to point to any subject record, chart, or form for subject 153743 that referred to IND **[redacted]**. Although the **[redacted]** letter indicates that Dr. **[redacted]** wrote Dr. **[redacted]** concerning **[redacted]** in 1990, it does not provide support for Dr. Vriesendorp's assertion that IND **[redacted]** and Dr. **[redacted]** investigator status under IND **[redacted]** were both still active in 1993 (three years after the **[redacted]** letter was written). Dr. Vriesendorp's mere allegations are not enough to overcome a properly supported motion for summary judgment. See, First Nat'l Bank v. Cities Serv. Co., 391 U.S. 253, 289 (1968). Dr. Vriesendorp should have used more caution before treating a subject with an experimental drug that he had not studied under an IND for more than three years. Taken into consideration with the fact that Dr. Vriesendorp was the author of the protocols for IND **[redacted]**, the above observations indicate that Dr. Vriesendorp, either willfully or in reckless disregard of his responsibilities as a principal investigator, administered the **[redacted]** without an effective IND.

Further undermining the credibility of Dr. Vriesendorp's assertions are his contradictory explanations for the source of the **[redacted]**. On the one hand, Dr. Vriesendorp claimed that he received the **[redacted]** from Dr. **[redacted]** who brought it with him to **[redacted]** from **[redacted]**. See, Dr. Vriesendorp's Request for Commissioner Review at 11 and CBER's Motion for Summary Decision, Ex. 2, p. 10-11. On the other hand, Dr. Vriesendorp admitted in a letter to Linda Collins, FDA, that he requested the **[redacted]** from **[redacted]** and that the sample was received at **[redacted]**. CBER's Motion for Summary Decision, Ex. 5, p.2 and Dr. Vriesendorp's Request for a Hearing, Ex. 16, p. 3. In addition, Dr. Vriesendorp can provide no written documentation for the source of

the **[redacted]**.

For all of these reasons, I find that there is no genuine and substantial issue of fact that Dr. Vriesendorp violated 21 CFR § 312.40(d) by administering **[redacted]** to a subject without an effective IND. [\[3\]](#) Additionally, I affirm Dr. McCormick's finding that Dr. Vriesendorp deliberately violated 21 CFR § 312.40(d). [\[4\]](#)

Charge 2: Protocol Violations

CBER charged that Dr. Vriesendorp failed to fulfill the general responsibilities of an investigator by deviating from the protocols for the study in several instances, in violation of 21 CFR § 312.60. This regulation requires the investigator to ensure that the clinical investigation is conducted according to the investigator statement (FDA Form 1572), the investigational plan, and applicable regulations. In addition, 21 CFR § 312.60 specifies that the investigator is responsible for the rights, safety, and welfare of subjects in his care. Both protocols **[redacted]** and **[redacted]** under IND **[redacted]** were written by Dr. Vriesendorp.

Charge 2a: Protocol Violations, Patient Eligibility Criteria

CBER charged that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR § 312.60 by providing investigational drugs to subjects who did not meet the protocol eligibility criteria. CBER cited to several deviations from protocol. In particular, CBER charged that Dr. Vriesendorp enrolled subjects with blood platelet counts below the required cutoff in protocols **[redacted]** and **[redacted]**; that he enrolled one subject with a Zubrod performance status above the required cutoff; that he enrolled a subject who could not have passed the required pulmonary function test under protocol **[redacted]**; that he enrolled a subject in both protocols with granulocyte counts below the required cutoff; and that he enrolled subjects who lacked a required life expectancy of greater than three months. CBER's Motion for Summary Decision at 11-12. CBER further provided evidence that these violations were deliberate: 1) Dr. Vriesendorp was an experienced investigator, 2) he was the author of both protocols, 3) he knew how to amend protocols, and 4) he knew how to obtain single patient INDs (often called "compassionate use INDs") to treat patients who did not meet the protocol eligibility requirements. Finally, CBER argued that by signing FDA Form 1572, Dr. Vriesendorp committed himself to follow all applicable regulations. Specifically, the form Dr. Vriesendorp signed includes a commitment that the investigator will not make changes in the research without Institutional Review Board (IRB) approval.

Dr. Vriesendorp acknowledged that certain patients were admitted to the clinical study who did not satisfy the patient eligibility criteria. [\[5\]](#) However, Dr. Vriesendorp asserted various medical justifications for deviating from patient eligibility requirements without obtaining prior approval from the IRB or without

obtaining a single patient IND. For instance, Dr. Vriesendorp admitted that he enrolled three subjects with platelet counts below the required cutoff based upon the "best clinical judgment of the medical team" and it was his team's "assessment...that the risks of withholding therapy were greater than the risks of their thrombopenia." CBER's Motion for Summary Decision, Ex. 2, p. 9. Furthermore, Dr. Vriesendorp argued that with regard to enrolling subjects with low platelet and granulocyte counts, "[h]ematological damage is not predicated by blood values such as platelet or granulocyte or red cell levels at study entry...This observation invalidates the generic application of minimum hematological parameters as an eligibility criteria." Vriesendorp's Opposition to CBER's Motion for Summary Decision at 36. Dr. Vriesendorp argued that he enrolled the patient with the low Zubrod score for "compassionate reasons." CBER's Motion for Summary Decision, Ex. 2, p. 3.

Pulmonary function tests were performed only sporadically because they were said to be expensive, unsafe, and uninformative and there was a risk of cross infection between sequential patients using the same pulmonary function test apparatus.

Vriesendorp's Opposition to CBER's Motion for Summary Decision at 38-39. Dr. Vriesendorp went on to claim that the removal of the pulmonary function test from the protocol should have been done earlier, but that he "forgot to do so until the deficiency was pointed out to me." CBER's Motion for Summary Decision, Ex. 2, p. 3. Subjects with a life expectancy of less than three months were treated off protocol "as an emergency, treatment use." CBER's Motion for Summary Decision, Ex. 2, p. 4. In addition, Dr. Vriesendorp cited a January 8, 1996 memo to **[redacted]** clinical faculty and others from **[redacted]**, M.D., Associate Vice President for Clinical and Translational Research, to support his position that **[redacted]** supported a principal investigator "override" that would allow only the principal investigator to enter a subject into the protocol who would otherwise be ineligible under the protocol's eligibility criteria; since he claims he was operating under **[redacted]** "override" policy, Dr. Vriesendorp argued that the deviations from the protocol were not deliberate. [\[6\]](#)

In his Summary Decision, Dr. McCormick found that there were no genuine issues of material fact for a hearing on Charge 2a and that Dr. Vriesendorp both repeatedly and deliberately violated 21 CFR § 312.60 by enrolling patients in violation of the protocols' eligibility criteria. Dr. McCormick found that the requirements in § 312.60 and the commitment Dr. Vriesendorp made by signing FDA Form 1572 did not allow for his unilateral deviation from the protocols' eligibility criteria nor did they create any legitimate confusion on this issue. Dr. McCormick also found that the medical issues related to the deviations should have been raised with the IRB before the deviations occurred. Finally, Dr. McCormick held that Dr. Vriesendorp's assertion of a principal investigator "override" privilege in the 1996 **[redacted]** memo had no basis in FDA's regulations and did not change the fact that Dr. Vriesendorp violated 21 CFR §

312.60 and the signed FDA Form 1572.

After reviewing the administrative record, I find that Dr. McCormick's conclusion that there is no genuine issue of fact that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR § 312.60 by providing the investigational drug to patients who did not meet the protocol eligibility criteria is appropriate and I affirm it. Contrary to Dr. Vriesendorp's assertion in his Request for Commissioner Review at 12, Dr. McCormick gave adequate consideration to Dr. Vriesendorp's explanations for the deviations. Further, Dr. Vriesendorp's reliance on the 1996 **[redacted]** memo to show that he did not deliberately violate 21 CFR § 312.60 is misplaced. [\[7\]](#) It is always an investigator's responsibility first and foremost to ensure compliance with FDA's regulations which have the force and effect of law. To the extent that a sponsor's policies may contradict or be inconsistent with these regulations, the investigator has a duty to fully comply with the regulations. It has been established in the record that, contrary to Dr. Vriesendorp's assertions of confusion or ignorance of FDA regulatory requirements, Dr. Vriesendorp was familiar with clinical study procedures as discussed above. Furthermore, Dr. Vriesendorp signed FDA Form 1572 in which he committed to follow all applicable FDA regulations. Therefore, I find that Dr. Vriesendorp repeatedly and deliberately deviated from the protocol eligibility requirements he authored without first obtaining IRB approval to amend the protocol.

Charge 2b: Protocol Violations, Platelet Stopping Criteria

CBER charged that Dr. Vriesendorp violated the platelet stopping criteria in protocol **[redacted]** by administering the **[redacted]** to eight subjects whose blood platelet counts were below specified levels.

In response, Dr. Vriesendorp admitted that some patients had platelet counts below that specified in the protocol. He argued that these patients had low counts because of the Hodgkin's disease and previous therapy. Vriesendorp's Opposition to CBER's Motion for Summary Decision at 35-36. He decided that he would treat these patients for whom no other therapeutic options existed. *Id.* Further, Dr. Vriesendorp claimed to rely on the 1996 **[redacted]** memo's principal investigator "override" function to justify his deviations of the protocol as not being deliberate. [\[8\]](#) *Id.*

In his Summary Decision, Dr. McCormick found that there were no genuine issues of fact for a hearing on Charge 2b and that Dr. Vriesendorp both repeatedly and deliberately violated 21 CFR § 312.60 by enrolling patients with platelet counts below those specified in the protocol. Dr. McCormick found that Dr. Vriesendorp failed to inform the IRB of his deviations as required under FDA Form 1572 which he signed.

I am persuaded by the evidence in the record that Dr. McCormick's finding on this charge was appropriate. The record is clear that Dr. Vriesendorp deliberately violated the protocol requirements which he authored. Dr. Vriesendorp's asserted reliance on the **[redacted]** principal investigator "override" policy, even if established, cannot alter the fact that he repeatedly violated the requirements of 21 CFR § 312.60 and FDA Form 1572 by unilaterally deviating from the study protocol. Therefore, I find that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR § 312.60 by enrolling patients with platelet counts below those specified in the protocol.

Charge 2c: Protocol Violations, Concurrent Therapy

CBER charged that Dr. Vriesendorp deviated from both protocols by the administration of two concurrent therapies to five patients.

In response, Dr. Vriesendorp admitted administering the concurrent therapies to five patients. However, he argued that since the protocols were silent on the use of concurrent therapies, he cannot be accused of deliberately violating the protocols.

In his Summary Decision, Dr. McCormick found that there were no genuine issues of fact for a hearing on Charge 2c and that Dr. Vriesendorp both repeatedly and deliberately violated 21 CFR § 312.60 by administering concurrent therapies that were not approved under the protocols. In particular, Dr. McCormick found that Dr. Vriesendorp's interpretation that the protocol's failure to prohibit concurrent therapies meant that any concurrent therapy is permitted was unreasonable since it could render the study results impossible to evaluate and expose patients to unnecessary risk while still technically following the protocol. Dr. McCormick also found that Dr. Vriesendorp's conduct, described above, showed a reckless disregard for the protocol requirements. Dr. McCormick also relied on a letter, dated January 17, 1990, from Dr. **[redacted]** to Dr. Vriesendorp (when they were both at **[redacted]**). This letter warned Dr. Vriesendorp that the use of a concurrent therapy in the study in which they were participating in 1990 would violate the protocol and therefore supports Dr. McCormick's finding that Dr. Vriesendorp's use of concurrent therapies not authorized in the protocols under IND **[redacted]** was deliberate.

After reviewing the administrative record, I affirm Dr. McCormick's findings for this charge. The record shows that Dr. Vriesendorp deliberately and repeatedly violated 21 CFR § 312.60 by administering concurrent therapies not listed in the protocols. Dr. Vriesendorp's conduct is shows a reckless disregard for the protocols' requirements and for the requirement of amending the protocols through the IRB. If Dr. Vriesendorp's interpretation were carried out to its logical conclusion, then in any study under an IND an investigator could administer any investigational new drug that would otherwise have never been approved by an

IRB or permitted by the FDA to be studied in human subjects. That result would be absurd. In Dr. Vriesendorp's Request for Commissioner Review at 14, he claims that "[i]f treatment were likely to confound the study results, that treatment would have been duly noted and prohibited by the sponsor's protocol." This is an unreasonable argument, however, since the sponsor and the IRB cannot have knowledge of every possible concurrent therapy an investigator might choose to employ that might skew the study's results or threaten subject safety. One of the IRB's functions is to determine whether proposed therapies are likely to be safe for subjects and of scientific value to investigators. In his unilateral use of concurrent therapies, I find that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR § 312.60 by deviating from protocol without first obtaining IRB approval, obtaining single patient INDs, or obtaining a new IND for the several subjects.

Charge 2f: Protocol Violations, Safety Testing

CBER charged that Dr. Vriesendorp deviated from protocol **[redacted]** by failing to perform the required **[redacted]** test for **[redacted]** in any of his subjects. CBER further alleged that this violation of 21 CFR § 312.60 was deliberate since Dr. Vriesendorp knowingly chose not to perform the test and he did not attempt to change the protocol.

In response, Dr. Vriesendorp agrees that he did not perform the test but explains that he found it was unnecessary and did not contribute to patient safety. In Dr. Vriesendorp's Request for Commissioner Review at 16, he claims that **[redacted]**'s principal investigator "override" policy made him believe that such a deviation from protocol was possible; therefore, he alleges that these deviations were not deliberate.

In his Summary Decision, Dr. McCormick found that there were no genuine issues of fact for a hearing on Charge 2f and that Dr. Vriesendorp both repeatedly and deliberately violated 21 CFR § 312.60. Dr. McCormick found that Dr. Vriesendorp failed to perform the required **[redacted]** test for **[redacted]** and that "his after the fact justification is inadequate to raise a factual issue for the hearing." Summary Decision of the Presiding Officer at 26.

After reviewing the administrative record, I find that Dr. McCormick's conclusion that there is no genuine and substantial issue of fact that Dr. Vriesendorp violated 21 CFR § 312.60 by failing to perform the required **[redacted]** test as specified in protocol **[redacted]** is appropriate and I affirm it. It is undisputed that Dr. Vriesendorp did not give the test to any of the subjects, in violation of the protocol's written requirements and 21 CFR § 312.60. The fact that Dr. Vriesendorp did not believe that the test was necessary is not a sufficient justification for failing to amend the protocol with the IRB. My evaluation of Dr. Vriesendorp's "principal investigator override" policy argument is discussed above

under Charge 2a; again, Dr. Vriesendorp may not rely on this alleged policy when he violated the requirements of 21 CFR § 312.60 and FDA Form 1572 by unilaterally deviating from the study protocol. Therefore, I find that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR § 312.60 by failing to perform the required **[redacted]** test.

B. Factual Disputes on Four Charges that are Contested by CBER

Charge 2e: Administration of [redacted] Without an Appropriate Imaging Study

CBER charged that Dr. Vriesendorp deviated from section 5.4 of protocol **[redacted]** by administering **[redacted]** without an appropriate imaging study with **[redacted]**, thus exposing subject 153743 to unnecessary risk caused by the presence of **[redacted]**. According to section 5.4, before a subject receives the treatment dose of **[redacted]**, the investigator must conduct an imaging study with **[redacted]**. CBER's Motion for Summary Decision, Ex. 26, p. 12. This **[redacted]** imaging study determines whether the subject would benefit from receiving the **[redacted]**. In this case, CBER charged that subject 153743 (the same subject in Charge 1 who was given the **[redacted]** without an IND in effect) received the **[redacted]** without Dr. Vriesendorp conducting the appropriate imaging study using **[redacted]** beforehand. Instead, Dr. Vriesendorp used a **[redacted]** to do the imaging study which CBER alleged was inadequate to determine whether a **[redacted]** would be effective. CBER's Motion for Summary Decision at 15-17. Therefore, CBER argued that Dr. Vriesendorp's failure to conduct the appropriate imaging test before treating the subject with the **[redacted]** dose unnecessarily exposed him to radiation and violated 21 CFR § 312.60's requirement that "[a]n investigator is responsible for...protecting the...safety [and] welfare of patients under the investigator's care."

In response, Dr. Vriesendorp admitted that the imaging study had not been done with the **[redacted]**, but rather with a dose of **[redacted]** which was given before the **[redacted]**. CBER's Motion for Summary Decision at 15-17 and Ex. 2, p. 7.

In his Summary Decision, Dr. McCormick found that there were no genuine issues of material fact on Charge 2e, that Dr. Vriesendorp did not violate 21 CFR § 312.60, and that Dr. Vriesendorp was entitled to summary decision as a matter of law. Dr. McCormick found that protocol **[redacted]** was limited to the use of **[redacted]** and that although section 5.4 of the protocol does not specify **[redacted]**, "it is clear that **[redacted]** is contemplated." Summary Decision of the Presiding Officer at 27. He found that Dr. Vriesendorp administered **[redacted]** to the subject in accordance with section 5.4, so he did not violate the protocol as CBER alleges. "Simply put, Dr. Vriesendorp could not have violated

Protocol **[redacted]** by failing to administer **[redacted]**, because the protocol called for administration of **[redacted]**.” Id. at 28.

CBER requested that the Commissioner review Dr. McCormick’s decision on the basis that Dr. Vriesendorp failed to protect the safety of the subject as required by 21 CFR § 312.60 by utilizing an imaging test using the **[redacted]** that could not adequately determine whether the subject would benefit from receiving the **[redacted]**. CBER’s Request for Commissioner Review at 2. “Although protocol **[redacted]** was approved for the study of **[redacted]**, the purpose of the imaging step remains valid: to establish tumor targeting for the particular **[redacted]** (**[redacted]**, etc.) to be used in the treatment dose, and to establish the absence of **[redacted]** to that particular **[redacted]**.” Id.

I have reviewed the administrative record, the Summary Decision, and CBER’s Request for Commissioner Review at 2-3. Although protocol **[redacted]** did not specify **[redacted]** for the imaging study, since the protocol was limited to the use of **[redacted]**, one can presume that the use of **[redacted]** for the imaging study was appropriate. However, for subject 153743, Dr. Vriesendorp went beyond protocol **[redacted]**’s requirements by administering **[redacted]** (for which he did not have an IND in effect). In this case, it is not clear whether the presumption that **[redacted]** is appropriate for the imaging study still applies. Although CBER argues that under the terms of Protocol **[redacted]**, the “imaging test is an obligatory safety requirement regardless of the source (**[redacted]**, **[redacted]**, etc.) of the **[redacted]**,” there is no factual evidence presented in the record that supports the position that the **[redacted]** treatment (through the **[redacted]** imaging test and the **[redacted]** treatment dose) must be of the same **[redacted]** origin (i.e. **[redacted]**) to be safe. Since I have already determined that Dr. Vriesendorp deliberately violated 21 CFR § 312.40(d) by administering **[redacted]** to a subject without an effective IND as discussed in Charge 1, I find that there is no reason to address an alleged violation concerning the use of **[redacted]** for the imaging study for the subject.

Charge 3a: Failure to Report Deaths to the IRB

CBER charged Dr. Vriesendorp with failure to report promptly to the IRB the deaths of two subjects in 1995 in violation of 21 CFR §§ 56.103(a) and 312.66. ^[9] The IRB approval letter, dated March 21, 1995, for protocol **[redacted]** specifically notified Dr. Vriesendorp that he was to promptly report “any death while patient is on study” to the IRB. CBER’s Motion for Summary Decision, Ex. 17. CBER further alleged that these violations were deliberate since the March 1995 IRB approval letter was clear in its reporting requirement and it was addressed to Dr. Vriesendorp himself. CBER’s Motion for Summary Decision pp. 22-23.

In response, Dr. Vriesendorp stated that the deaths were not caused by the investigational drug, that 21 CFR § 312.32(c)(1)(A) required reporting only serious and unexpected adverse reactions, [\[10\]](#) and that he was not made aware of the IRB's reporting requirements until April 1996. CBER's Motion for Summary Decision, Ex. 2, pp. 9-10.

In his Summary Decision, Dr. McCormick found that Dr. Vriesendorp did not report the two subject deaths as required under the IRB's written procedures. Further, he found that Dr. Vriesendorp's allegation of ignorance of the IRB's requirements was not credible in light of the fact that the March 1995 IRB approval letter was addressed specifically to him. However, Dr. McCormick focused solely on the requirement in 21 CFR § 312.66 that requires the reporting of "unanticipated problems" and that there was a genuine issue of material fact as to whether the deaths were "unanticipated."

CBER requested that the Commissioner review Dr. McCormick's decision on the basis that he failed to consider the other requirements of 21 CFR §§ 56.103(a) and 312.66 which mandate that an investigator assure continuing review and approval of studies by an IRB. [\[11\]](#) By failing to report these two deaths to the IRB as required by the March 1995 IRB approval letter, CBER argued that Dr. Vriesendorp prevented the IRB from conducting a continuing review of the study in violation of 21 CFR §§ 56.103(a) and 312.66. CBER's Request for Commissioner Review at 3.

After reviewing the administrative record, I do not accept the Presiding Officer's findings for Charge 3a. Instead, I believe that summary judgment for CBER is warranted here. The March 21, 1995 letter from the IRB to Dr. Vriesendorp granting him approval of protocol 95-004 specifically required him to promptly report "any death while patient is on study." CBER's Motion for Summary Decision, Ex. 17. It is undisputed that Dr. Vriesendorp did not report the two subject deaths to the IRB. Dr. Vriesendorp's failure to promptly inform the IRB of the deaths of his subjects (as he was required to do by the IRB's approval conditions) hindered the IRB's ability to continually review the study in violation of 21 CFR §§ 56.103(a) and 312.66. I also find that Dr. Vriesendorp deliberately violated 21 CFR §§ 56.103(a) and 312.66 since he had notice of the March 1995 IRB approval letter (which was specifically addressed to him) and he was an experienced investigator. Therefore, I find that Dr. Vriesendorp repeatedly and deliberately violated 21 CFR §§ 56.103(a) and 312.66 by failing to report the deaths of two subjects to the IRB.

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

CBER charged Dr. Vriesendorp with failure to report promptly to the IRB adverse reactions from the treatment of two subjects in violation of 21 CFR §§ 56.103(a)

and 312.66. Specifically, one subject developed Grade 4 thrombocytopenia within seven weeks after administration of the **[redacted]** under protocol **[redacted]** and the other subject developed bone marrow aplasia, fever, and subsequent fungal sepsis following the **[redacted]** administration under protocol **[redacted]**. CBER's Motion for Summary Decision, p. 22. The IRB approval letter, dated March 21, 1995, for protocol **[redacted]** specifically notified Dr. Vriesendorp that he was to promptly report "any severe adverse effects" to the IRB. CBER's Motion for Summary Decision, Ex. 17. CBER further alleged that these violations were deliberate.

In response, Dr. Vriesendorp argued that there were "no reportable adverse experiences" to inform the IRB. CBER's Motion for Summary Judgment, Ex. 2, p. 10. He further argued that that he was not aware of any serious and unexpected adverse effects reasonably caused by the drug. Id.

In his Summary Decision, Dr. McCormick found that Dr. Vriesendorp did not report the adverse reactions of the two subjects as required under the IRB's written procedures. However, Dr. McCormick focused solely on the requirement in 21 CFR § 312.66 that requires the reporting of "unanticipated problems" and that there was a genuine issue of material fact as to whether the adverse reactions were "unanticipated."

CBER requested that the Commissioner review Dr. McCormick's decision on the basis that he failed to consider the other requirements of 21 CFR §§ 56.103(a) and 312.66 which mandate that an investigator assure continuing review and approval of studies by an IRB. By failing to report these adverse reactions to the IRB as required by the March 1995 IRB approval letter, CBER argued that Dr. Vriesendorp prevented the IRB from conducting a continuing review of the study in violation of 21 CFR §§ 56.103(a) and 312.66. CBER's Request for Commissioner Review at 3-4.

After reviewing the administrative record, I do not accept the Presiding Officer's findings for Charge 3b. I believe that summary judgment for CBER is warranted here as to the failure to report the severe adverse reactions of one subject. [\[12\]](#) The March 21, 1995 letter from the IRB to Dr. Vriesendorp granting him approval of protocol **[redacted]** specifically required him to promptly report "any severe adverse effects." CBER's Motion for Summary Decision, Ex. 17. The IRB's approval of Dr. Vriesendorp's protocol was specifically conditioned on the reporting requirements which were clearly described in the letter. It is undisputed that Dr. Vriesendorp did not report the adverse reaction to the IRB. I believe that a competent investigator in this area of study would conclude that the conditions described above for subject 256063 are properly characterized as "severe." Aplasia refers to the "lack of development of an organ or tissue." Dorland's Illustrated Medical Dictionary (1994), p. 106. Sepsis is defined as "the presence

in the blood or other tissues of pathogenic microorganisms or their toxins.” Id. at 1507. Dr. Vriesendorp, as an experienced principal investigator, knew or should have known that these reactions were “severe” and he should have reported them to the IRB. The fact that he did not do so demonstrates a deliberate disregard of his duties as principal investigator for IND **[redacted]**. Dr. Vriesendorp’s failure to promptly inform the IRB of the severe adverse reactions of his subject (as he was required to do by the IRB’s approval conditions) hindered the IRB’s ability to continually review the study in violation of 21 CFR §§ 56.103(a) and 312.66. Therefore, I find that Dr. Vriesendorp deliberately violated 21 CFR §§ 56.103(a) and 312.66 by failing to report the adverse reactions of one subject.

Charge 6a: Informed Consent, Low Blood Cell Counts

CBER alleged that Dr. Vriesendorp failed to obtain appropriate informed consent in violation of 21 CFR § 312.60 (which references the provisions of 21 CFR Part 50). CBER agreed that the informed consent form was adequate in describing “any reasonably foreseeable risks...to the subject,” 21 CFR § 50.25(a)(2), when it included the statement that “blood counts will return to pretreatment levels but might require additional measures.” CBER argued, however, that for the subjects who were enrolled in the study in violation of the protocol’s platelet eligibility requirements, the consent form that was used for patients who met the protocol platelet criteria was inadequate for proper informed consent under 21 CFR § 50.25(a)(2).

In his Summary Decision, Dr. McCormick found that Dr. Vriesendorp had raised an issue as to whether patients with lower platelet levels would be likely to experience long-term low blood cell counts. Therefore, Dr. McCormick found that there was a genuine issue of material fact for a hearing for Charge 6a.

CBER requested that the Commissioner review Dr. McCormick’s decision on this charge on the basis that “for the patients who did not meet the study entry criteria, the consent form did not meet the requirements of part 50 and was, therefore, inadequate.” CBER’s Request for Commissioner Review at 4.

Based upon my review of the record in this case, I find that Dr. McCormick acted appropriately by not reaching this charge. I believe that summary judgment for CBER is not warranted by the facts. Dr. Vriesendorp violated both the protocols and 21 CFR § 312.60 by enrolling subjects whose platelet levels were below the protocol’s eligibility requirements (see Charge 2b above). Furthermore, it is undisputed that the same consent form was given to the two different patient populations even though the below-protocol level patients might have been subject to different foreseeable risks. Dr. McCormick denied summary judgment on this charge on the ground that Dr. Vriesendorp raised the issue as to whether it was foreseeable that these below-protocol level patients would experience

long-term low blood cell counts. There is no evidence in the record to show that either Dr. Vriesendorp or the IRB assessed the particular foreseeable risks to those subjects with below-protocol platelet counts before enrolling them in the study. It is possible, however, that Dr. Vriesendorp did not do so because the risks were not foreseeable to him at the time he obtained the subjects' consent. In any case, on this record, the issue of foreseeability here presents a genuine issue of fact for a hearing. However, since the findings of the other charges are sufficient to warrant disqualification, it is unnecessary to hold a hearing on Charge 6a.

C. Other Charges

In addition to the above charges, CBER charged that Dr. Vriesendorp failed to fulfill the general responsibilities of an investigator by administering a fractionated (divided) dose of an investigational new drug in contradiction of the protocol's requirements, in violation of 21 CFR § 312.60 (Charge 2d); failed to fulfill the general responsibilities of an investigator by deviating from the protocols by failing to perform dosimeter calculations, in violation of 21 CFR § 312.60 (Charge 2g); failed to maintain adequate and accurate records relating to the investigational new drugs, in violation of 21 CFR §§ 312.60, 312.62 (Charge 4); failed to prepare and submit investigator reports by failing to report certain adverse reactions to the sponsor, in violation of 21 CFR § 312.64 (Charge 5); and failed to obtain informed consent because of misleading statements in the consent form regarding safety testing to detect the development of **[redacted]**, in violation of 21 CFR Part 50 and 21 CFR § 312.60 (Charge 6b).

As discussed in detail in the Presiding Officer's summary decision, Dr. McCormick found that he could not make a determination on these charges without further evidence and denied CBER's Motion for Summary Decision on these charges.

Neither CBER nor Dr. Vriesendorp has requested that I review Dr. McCormick's decision on these charges and I, accordingly, have not done so.

D. Summary of Findings

Based upon the above analysis, I conclude that there is no genuine and substantial issue of fact with regard to whether Dr. Vriesendorp failed to fulfill the responsibilities of an investigator by deviating from the study protocols in several instances, by failing to report the deaths and severe adverse effects of the IND, and by administering an IND to a subject in the absence of an effective IND, in violation of 21 CFR Parts 56 and 312. Under 21 CFR § 312.70, my findings on Charges 1, 2a, 2b, 2c, 2f, 3a, and 3b are sufficient to disqualify Dr. Vriesendorp.

III. DR. VRIESENDORP'S REQUEST FOR REVIEW OF THE SUMMARY DECISION

As noted earlier, in addition to contesting several factual issues in the charges as discussed above, Dr. Vriesendorp requested that I review the Presiding Officer's summary decision on several grounds. First, Dr. Vriesendorp argues that Dr. McCormick applied an incorrect standard of proof. Second, Dr. Vriesendorp argues that Dr. McCormick ignored inferences favoring him and embraced inferences supporting CBER, contrary to caselaw holding that in deciding summary judgment motions, all reasonable inferences must be drawn in favor of the non-moving party. Third, Dr. Vriesendorp argues that Dr. McCormick gave the term "deliberately" a meaning that is inconsistent with its common usage. Fourth, Dr. Vriesendorp alleges that he did not receive all the information he asked for in a Freedom of Information Act (FOIA) request related to FDA's 1996 investigation of IND [redacted]. Finally, Dr. Vriesendorp argues that the violations he was charged with were not material to warrant disqualification.

A. Standard of Proof

Dr. Vriesendorp argues that CBER has the burden of establishing any violations of FDA regulations by "clear and convincing evidence" due to the seriousness of the sanctions imposed by disqualification (i.e., bar Dr. Vriesendorp from receiving investigational new drugs).

I find that Dr. Vriesendorp is incorrect; the "preponderance of the evidence" standard applies in clinical investigator disqualification hearings. See, Commissioner's Decision, In the Matter of Boyles, M.D. at 4 (1995). As discussed above, applying this preponderance of the evidence standard, I found that Dr. Vriesendorp either repeatedly and/or deliberately violated FDA regulations in Charges 1, 2a, 2b, 2c, 2f, 3a, and 3b. However, even if one were to use the "clear and convincing evidence" standard of proof, the evidence shows that Dr. Vriesendorp repeatedly (more than once) violated 21 CFR Parts 56 and 312 in Charges 2a, 2b, 2c, 2f, and 3a. Under 21 CFR § 312.70, a finding that either a repeated or deliberate violation occurred is a sufficient basis for disqualification. In fact, Dr. Vriesendorp admits that he repeatedly violated the protocol requirements as specified in Charges 2a, 2b, and 2f. Therefore, disqualification of Dr. Vriesendorp is warranted for these charges under either the "preponderance of the evidence" or the "clear and convincing evidence" standard of proof.

B. Reasonable Inferences Must Be Drawn in Favor of the Non-Moving Party

Dr. Vriesendorp argues that Dr. McCormick ignored inferences favoring him and embraced attenuated inferences supporting CBER, contrary to caselaw holding that in deciding a motion for summary decision, all reasonable inferences must be drawn in favor of the non-moving party. Specifically, Dr. Vriesendorp argues that he submitted "voluminous documentation in support of his claims, yet this submission was virtually ignored by the Presiding Officer." Vriesendorp's Request

for Commissioner Review at 20-21. I find that this statement is without merit. Dr. McCormick refers to Dr. Vriesendorp's documentary evidence in numerous places throughout his summary decision (including letters written by Dr. Vriesendorp himself that were submitted as exhibits to CBER motions). Furthermore, Dr. McCormick also discussed throughout the summary decision the arguments that Dr. Vriesendorp put forth to try to explain his protocol and other deviations. The fact that Dr. McCormick found that a determination could not be made without further evidence and that summary judgment was not warranted at that stage for charges 2d, 2g, 3a, 3b, 4, 5, 6a, and 6b shows that he carefully examined the record for each party on each individual charge.

C. Meaning of "Deliberately"

Dr. Vriesendorp argues that Dr. McCormick misinterpreted the term "deliberately" in his opinion by holding that "deliberate" violations are those in "reckless disregard of the regulations' requirements." Dr. Vriesendorp's Request for Commissioner Review at 8. Dr. Vriesendorp believes that "deliberate" in the context of 21 CFR § 312 "can only mean that the investigator was aware of the obligations imposed by the FDA regulations and the investigator consciously chose to disregard and/or violate them." Vriesendorp's Request for Commissioner Review at 9 (emphasis in original). In addition, Dr. Vriesendorp argues that it is improper for the Presiding Officer to make credibility determinations regarding disputed issues of fact since summary judgment is not the proper vehicle for resolving credibility issues. For instance, Dr. Vriesendorp argues that, for Charge 1, it was improper for the Presiding Officer to make a credibility determination about his belief that he was operating under an effective IND when he administered the **[redacted]**, and thus not deliberately violating 21 CFR § 312.40(d). Id. at 11.

Dr. McCormick found that Dr. Vriesendorp acted deliberately because he acted with a reckless disregard for the study's requirements and for the safety of the study subjects. Summary Decision of the Presiding Officer at 14, 25, and 39-40. Dr. McCormick's interpretation of deliberate is consistent with the interpretation of "deliberately" given in previous disqualifications. [\[13\]](#) Even without this precedent, however, it is wholly reasonable to view deliberate as being established when it is shown that the clinical investigator engaged in reckless conduct.

Deliberate includes willful. See, Black's Law Dictionary 426, 1270 (6th ed. 1990). In McLaughlin v. Richland Shoe Co., the Supreme Court stated that "[i]n common usage the word 'willful' is considered synonymous with...'deliberate'...." 486 U.S. 128, 133 (1988). The Court found that willful conduct could be viewed as conduct demonstrating reckless disregard. Id. "[S]ince, however, [willful or reckless conduct] is almost never admitted, and can be proved only by the conduct and the circumstances, an objective standard must of necessity in

practice be applied.” W. Page Keeton, et al., Prosser and Keeton on Torts §34 at 213 (5th ed. 1984).

When a clinical investigator engages in conduct that he or she knew failed to comply with FDA’s regulations, or engages in conduct that showed reckless disregard for whether his or her conduct complied with FDA’s regulations, he or she is liable to being found to have “deliberately” violated the regulations. Similarly, an investigator whose conduct shows a reckless disregard for whether his or her conduct may result in a regulatory violation is liable to being found to have “deliberately” violated the regulations. Thus, Dr. Vriesendorp’s proposed definition— “the investigator was aware of the obligations imposed by the FDA regulations and the investigator consciously chose to disregard and/or violate them”—is too restrictive. In any event, a deliberate regulatory violation may be found in the absence of knowledge that a regulatory violation would occur, or in the absence of any specific intent to cause such a violation.

McLaughlin is useful in trying to give meaning to the word “deliberately” in the context of FDA’s regulations. With this particular disqualification, the standard that Dr. McCormick applied involved examining Dr. Vriesendorp’s conduct to determine whether Dr. Vriesendorp recklessly disregarded the requirements governing the use of an investigational new drug in human subjects.

Dr. McCormick found that Dr. Vriesendorp acted deliberately based on evidence in the record that demonstrated that Dr. Vriesendorp was well aware of the requirements listed in the study protocols. The record included evidence that showed that Dr. Vriesendorp authored the protocols for IND **[redacted]**, was the principal investigator for the protocols, was aware of the appropriate process to amend the 1992 protocol, and was aware of how to obtain single patient INDs for individual patients who did not meet the study eligibility requirements. In addition, Dr. Vriesendorp stated that he “served several times as a reviewer for the IRB for studies of other investigations.” Dr. Vriesendorp’s Motion for Summary Decision at 4. This evidence shows that when Dr. Vriesendorp violated FDA regulations, he did so willfully or in reckless disregard of clinical investigator requirements.

In his report of summary decision, Dr. McCormick found that there was no genuine and substantial issue of fact as to whether Dr. Vriesendorp deliberately violated 21 CFR §§ 312.40(d) and 312.60 (see discussion of Charges 1, 2a, 2b, 2c, and 2f above). Based upon my review of the record, I affirm Dr. McCormick’s finding on these charges and on his interpretation of the term “deliberately.”

D. Dr. Vriesendorp’s Access to Records Possessed by FDA

Dr. Vriesendorp submitted to the record letters in which he requested via the Freedom of Information Act (FOIA) all documents related to FDA’s 1996

investigation of IND **[redacted]**. FDA subsequently responded in 1999 by providing all requested documents except for 115 pages of material which were determined to be either non-responsive to the request or not releaseable. Dr. Vriesendorp argues that lack of access to these pages “unfairly prevented him from the opportunity to prepare an adequate response to CBER’s allegations” and deprived him of his due process rights. Vriesendorp’s Request for Commissioner Review at 20.

Dr. McCormick considered this argument and rejected it since Dr. Vriesendorp had full access to all documents CBER relies on for summary decision. Summary Decision of the Presiding Officer at 6-7. Dr. Vriesendorp claims an absolute right of access which is unsupported in law. Even for criminal defendants, for whom a liberty or life interest is at stake, there is no “full-scale, constitutionally-mandated discovery right.” Spicer v. Roxbury Correctional Institute, 194 F.3d 547, 555 (4th Cir. 1999). Mere allegations of missing documents are not enough to overcome a properly supported motion for summary judgment. See, First Nat’l Bank v. Cities Serv. Co., 391 U.S. 253, 289 (1968). Based upon my review of the record, I affirm Dr. McCormick’s decision and find that appropriate due process considerations were implemented in the summary decision.

E. Materiality of the Violations

Dr. Vriesendorp argues that you should not concur in Dr. McCormick’s recommendation that he be disqualified because “there is no evidence that any patients suffered adverse consequences as a result of the alleged deviations” from the written IND protocols. Dr. Vriesendorp’s Request for Commissioner Review at 7. Dr. Vriesendorp believes that since there were no injuries to the subjects from the deviations and some showed a positive response to the treatment, they cannot be material and should not be the basis for his disqualification. [\[14\]](#)

Once a finding is made that an investigator has repeatedly or deliberately failed to comply with the applicable requirements, disqualification generally must follow. The regulations provide little discretion for alternative resolution. In the preamble to 21 CFR §312.70, FDA rejected the option of lesser sanctions, providing instead that disqualification would be the general response to violations. 52 Fed.Reg. 8798, 8826 (1987). However, the preamble does provide that the Commissioner always retains the discretion not to disqualify if the Commissioner believes the violations are insignificant or lesser sanctions would be adequate. *Id.* The preamble makes clear that this discretion should be exercised only in extraordinary circumstances (e.g., where the violations are truly insignificant, or where disqualification would be truly unjust or would accomplish nothing). See also, In the Matter of James A. Halikas, M.D. (2001) at 28.

Given the findings in this matter, such extraordinary circumstances do not exist.

I find that Dr. Vriesendorp repeatedly and deliberately violated IND **[redacted]**'s written protocols which Dr. Vriesendorp himself authored. Dr. Vriesendorp also failed to report deaths and severe adverse effects of the IND to the IRB for its continuous review of the protocol. Furthermore, Dr. Vriesendorp gave an investigational new drug, the **[redacted]** antibodies, to a subject in the absence of a valid IND. I find that these violations are sufficiently serious and numerous so as to require disqualification.

IV. CONCLUSION

Therefore, I conclude that Dr. Vriesendorp is no longer entitled to receive investigational drugs. Dr. Vriesendorp may seek to have his eligibility to receive investigational drugs reinstated pursuant to 21 CFR § 312.70(f).

/s/

Bernard A. Schwetz, D.V.M., Ph.D.
Acting Principal Deputy Commissioner

Dated: December 31, 2001

Footnotes□

¹ Dr. Vriesendorp's claim of ignorance is contradicted by two letters provided by CBER. The first, dated October 4, 1990, is from Dr. **[redacted]** to FDA. In this letter, Dr. **[redacted]** notified FDA that Dr. Vriesendorp had been removed as an investigator under IND **[redacted]**. The second letter, dated April 15, 1996, from Dr. **[redacted]** to FDA, states that no one was authorized to conduct any investigations of **[redacted]** under IND **[redacted]** outside of **[redacted]**. Although these letters themselves do not show actual notice of Dr. Vriesendorp's removal from participation as an investigator under IND **[redacted]**, they undercut his claim that he was never given notice of this removal. It seems implausible that Dr. **[redacted]** in October 1990 notified the FDA that Dr. Vriesendorp had been removed as an investigator under IND **[redacted]** but would neglect to inform Dr. Vriesendorp of this decision.

² 21 CFR § 312.20 applies to sponsors and not to investigators. Since Dr. Vriesendorp is not the sponsor of the study, he did not violate § 312.20 as Dr. McCormick found. The sponsor of the study was the **[redacted]**

³ Even Dr. Vriesendorp stated in his response that "in retrospect, I agree that an IND for this product [the **[redacted]**] should have been obtained." CBER's

Motion for Summary Decision, Ex. 2, p. 2.

⁴ The issue Dr. Vriesendorp has raised regarding the appropriate meaning of the term "deliberately" is discussed in Section III.C. of this decision.

⁵ "Dr. Vriesendorp readily admits that he did make mistakes in the execution of his responsibilities as an investigator." Dr. Vriesendorp's Opposition to CBER's Motion for Summary Decision at 57. "Vriesendorp admits that his oversights have broken rules or regulations." *Id.* at 58.

⁶ See Section III.C. of this decision for a discussion of the term "deliberately."

⁷ In addition, Dr. McCormick found that Dr. Vriesendorp did not properly abide by **[redacted]**'s interpretation of the "override" policy. See, Summary Decision of the Presiding Officer at 21.

⁸ In Dr. Vriesendorp's Request for Commissioner Review at 13, he also contends that "this alleged deviation was not material" since no patients were injured or died from uncontrolled bleeding. There is, however, no requirement for a finding of a "material" violation as a predicate to disqualification nor do the regulations specify that only a "material" violation warrants disqualification. See Section III.E. of this decision for a further discussion of the materiality of Dr. Vriesendorp's violations.

⁹ 21 CFR § 56.103(a) reads in part: "...any clinical investigation which must meet the requirements for prior submission...to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB..." 21 CFR § 312.66 reads in part: "[a]n investigator shall assure that an IRB...will be responsible for the initial and continuing review and approval of the proposed clinical study..."

¹⁰ Dr. Vriesendorp is mistaken. 21 CFR § 312.32 applies to sponsors only and not to investigators.

¹¹ 21 CFR § 56.103(a) reads in part: "...any clinical investigation...remains subject to continuing review by, an IRB..." 21 CFR § 312.66 reads in part: "...[a]n investigator shall assure that an IRB...will be responsible for the initial and continuing review of the proposed clinical study..."

¹² In its Motion for Summary Decision, CBER charged Dr. Vriesendorp with a repeated failure to report the severe adverse reactions of two subjects. CBER's Motion for Summary Decision at 21-22. Subject 140882 developed Grade 4 thrombocytopenia within seven weeks after administration of **[redacted]** under protocol **[redacted]**. *Id.* at 22. Subject 256063 developed complete bone

marrow aplasia, fever, and subsequent fungal sepsis following **[redacted]** administration under protocol **[redacted]** . Id. The March 1995 IRB approval letter for protocol **[redacted]** required Dr. Vriesendorp to promptly report "any severe adverse effects" to the IRB. The record is clear that he failed to report the severe adverse effects to the IRB for subject 256063 (even though the aplasia and fungal sepsis were serious adverse conditions) as required by the IRB approval letter for protocol **[redacted]** , thus preventing the IRB's continual review of the study in violation of 21 CFR §§ 56.103(a) and 312.66. However, CBER did not provide in the record a copy of the IRB approval letter for protocol **[redacted]** . Therefore, it is not clear whether Dr. Vriesendorp had any obligation to report "any severe adverse effects" to the IRB for subject 140882 under protocol **[redacted]** . Therefore, I do not find that Dr. Vriesendorp repeatedly violated 21 CFR §§ 56.103(a) and 312.66.

¹³ See, e.g., Commissioner's Decision: In the Matter of Halikas, M.D. (2001); Reports of the Presiding Officer: In the Matter of John H. Hopkinson III, M.D. (1982); In the Matter of Martin S. Mok, M.D. (1982).

¹⁴ In Dr. Vriesendorp's Request for Commissioner Review at 6, he asserts that there is a "requirement that the violations complained of, and upon which the disqualification is based, be material. That is, before an investigator can be disqualified, the Commissioner must find that the violations are material." However, there is no such materiality requirement in the clinical investigator regulations.