



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

William H. Ziering, M.D.
2963 Cormorant Road
Pebble Beach, CA 93953

MAY 20 2008

Notice of Disqualification of Eligibility to Receive Investigational Drugs

Dear Dr. Ziering:

I have reviewed the record of the regulatory hearing involving William H. Ziering, M.D., the summary decision of the Presiding Officer, the parties' summary decision memoranda with attachments, your submission requesting review of the summary decision, and additional judicially noticed records. Based on my review, I have concluded that you repeatedly and deliberately violated 21 C.F.R. Part 312 in connection with investigational new drug studies you conducted at your research facility, Central California Research Institute. Consistent with 21 C.F.R. § 312.70(b), I have determined that you are no longer eligible to receive investigational drugs. Under authority delegated to me by the Commissioner of Food and Drugs, I am issuing this Commissioner's Decision disqualifying you from eligibility to receive investigational drugs. The reasons for my determination are set forth in the enclosed decision.

You may seek to have your eligibility to receive investigational drugs reinstated pursuant to 21 C.F.R. § 312.70(f) upon presentation of adequate assurances that you will use investigational drugs solely in compliance with the provisions of 21 C.F.R. Parts 50, 56, and 312.

Sincerely,

Murray M. Lumpkin, M.D.
Deputy Commissioner
International and Special Programs

Enclosure

cc: Henry H. Startzman III, M.D.
Presiding Officer

Office of the Chief Counsel, GCF-1
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
REGULATORY HEARING ON THE PROPOSAL TO DISQUALIFY
WILLIAM H. ZIERING, M.D.
FROM RECEIVING INVESTIGATIONAL NEW DRUGS

COMMISSIONER'S DECISION

The purpose of this proceeding is to determine, pursuant to 21 C.F.R. § 312.70 and 21 C.F.R. Part 16, whether William H. Ziering, M.D., a clinical investigator, should be disqualified from receiving investigational new drugs. Henry H. Startzman III, M.D., served as the presiding officer for this disqualification. Dr. Startzman issued a summary decision in favor of the Center for Drug Evaluation and Research ("CDER") and recommended that Dr. Ziering be disqualified.

Under authority delegated to me by the Commissioner of Food and Drugs, I am issuing the Commissioner's Decision in this matter. Based on my review of the administrative record in this matter, including Dr. Startzman's Summary Decision, the parties' submissions, and other judicially noticed records, I conclude that Dr. Ziering repeatedly and deliberately violated the regulations governing clinical investigations. Therefore, I am disqualifying Dr. Ziering from receiving investigational drugs. The reasons for my decision follow.

I. PROCEDURAL BACKGROUND

The charges in this proceeding arise from an investigation conducted by the Food and Drug Administration ("FDA") of studies conducted by Dr. Ziering at his research facility, Central

California Research Institute ("CCRI"), in Fresno, California. Dr. Ziering, a specialist in allergy and pulmonary care, served as president and principal investigator of clinical research studies at CCRI during the time in question. CCRI was operated by Dr. Ziering in conjunction with his clinical practice center, the Ziering Allergy and Respiratory Center.

On March 14, 1995, counsel for CCRI sent a letter to FDA reporting personnel problems at CCRI. The letter provided information on an ongoing internal audit at CCRI and described remedial steps being taken to address the problems identified. FDA inspected Dr. Ziering's operations at CCRI between April 12 and May 16, 1995. At the conclusion of their inspection on May 24, 1995, the FDA investigators issued Dr. Ziering a List of Inspectional Observations ("Form FDA-483") containing 44 observations of deficiencies noted by the investigators during the inspection. On July 11, 1995, Dr. Ziering responded in writing to the observations in the Form FDA-483. FDA investigators later returned to CCRI and conducted a limited inspection between October 7 and 15, 1998.

The six CCRI studies reviewed by FDA that are now at issue in this proceeding are:

- A. Protocol [] "A Placebo-Controlled, Double-Blind Study of [] Aqueous Nasal Spray in Pediatric Patients with Spring Grass Seasonal Allergic Rhinitis," sponsored by []
- B. Protocol [] "A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Evaluation of the Safety, Efficacy and Effect on Asthma Quality of Life ('AQL') of Salmeterol in Subjects Receiving Inhaled Corticosteroids," sponsored by Glaxo Pharmaceuticals
- C. Protocol [] "A Randomized, Double-Blind, Double-Dummy, Parallel Group, Comparative Trial of Inhaled, Fluticasone Propionate Rotadisks via Diskhaler 500 mcg BID, Multi-Dose Powder Inhaler 500 mcg BID, and Placebo in Adolescent and Adult Patients with Mild to Moderate Asthma," sponsored by Glaxo Research Institute

- D. Protocol [] "An Open-Label Study of Fluvastatin in the Treatment of Patients with Hypercholesterolemia in Clinical Practice Settings," sponsored by Sandoz Pharmaceuticals
- E. Protocol [] "A Multicenter, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of Oral Twice Daily Administration of [] in Patients with Mild to Moderate Asthma," sponsored by []
- F. Protocol [] "A Randomized, Double-Blind, Parallel Group Trial to Assess the Topical Versus Systemic Efficacy of Fluticasone Propionate Rotadisks Via Diskhaler 500 MCG BID, 100 MCG BID, Fluticasone Propionate Tablets 20 MG QD, and Placebo in Adult Patients With Moderate Asthma," sponsored by Glaxo Pharmaceuticals

FDA issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain letter to Dr. Ziering on November 6, 1998. Dr. Ziering responded in writing on December 4, 1998. Through a Notice of Opportunity for Hearing (NOOH) issued on August 16, 1999, FDA's Associate Commissioner for Regulatory Affairs informed Dr. Ziering that he would be given an opportunity for a regulatory hearing under 21 C.F.R. Part 16 to determine whether he should be disqualified from receiving investigational new drugs. On September 8, 1999, Dr. Ziering responded to the NOOH in writing and requested a hearing. In a motion filed on September 7, 1999, CDER moved for summary decision on the following four charges against Dr. Ziering:

- (1) submission of false information in reports required to be submitted to the sponsor, in violation of 21 C.F.R. § 312.70(b);
- (2) failure to maintain adequate and accurate case histories, in violation of 21 C.F.R. § 312.62(b);
- (3) failure to follow the investigational plan, in violation of 21 C.F.R. § 312.60; and

- (4) failure to personally conduct or supervise the investigation(s), in violation of 21 C.F.R. § 312.53(c)(1)(vi)(c).

Counsel for Dr. Ziering filed a response on November 9, 2000, asking that CDER's motion be denied and reiterating Dr. Ziering's request for a hearing.¹

Pursuant to 21 C.F.R. § 16.26(b), the presiding officer may issue a summary decision on any issue when there is no genuine and substantial issue of fact regarding that issue and the moving party is entitled to judgment as a matter of law. Dr. Startzman reviewed the evidence presented in CDER's motion for a summary decision and Dr. Ziering's opposition to CDER's motion, which incorporates by reference Dr. Ziering's September 8, 1999 response to the NOOH. On March 4, 2003, Dr. Startzman issued a summary decision ("Summary Decision") in favor of CDER on two of the four charges.

Specifically, Dr. Startzman found that there were no genuine and substantial issues of fact with respect to Charge 2, that Dr. Ziering had repeatedly and deliberately failed to maintain adequate and accurate case histories, see 21 C.F.R. § 312.62(b), and Charge 3, that Dr. Ziering had repeatedly and deliberately failed to follow the investigational plan, see 21 C.F.R. § 312.60. Dr. Startzman therefore issued a summary decision in favor of CDER on those charges. With respect to Charge 1, submission of false information in required reports to the sponsor, see 21 C.F.R. § 312.70(b), Dr. Startzman found that a determination could not be made without further evidence and denied CDER's motion for summary decision on that charge. With respect to Charge 4, failure to personally conduct or supervise the investigation(s), see 21 C.F.R.

¹ The date of Dr. Ziering's response was incorrectly identified in Dr. Startzman's summary decision as having been filed on October 9, 2000.

§ 312.53(c)(1)(vi)(c), Dr. Startzman found that the regulation at issue was inapplicable to Dr. Ziering, and that, in any event, Dr. Ziering had not received adequate notice of the charge against him. Dr. Startzman therefore denied CDER's motion for summary decision on Charge 4 as well. Based upon his findings with respect to Charges 2 and 3, Dr. Startzman recommended that I disqualify Dr. Ziering.

On April 28, 2003, Dr. Ziering requested that I review the Summary Decision and not concur in Dr. Startzman's recommendation. Though Dr. Ziering's 56-page *pro se* submission does not specifically reference any of the charges against him, a fair reading of his submission suggests that he disputes Dr. Startzman's factual findings with respect to the two charges upon which Dr. Startzman based his disqualification determination.² In addition, Dr. Ziering also argues that: (1) "Dr. Startzman was handicapped in the dearth of materials at his disposal" in reaching the Summary Decision; (2) the standard that "the Principal Investigator is 'ultimately responsible' . . . must be interpreted in the context of the intent" of the investigator; and (3) disqualification is inappropriate in light of the fact that Dr. Ziering investigated as soon as he learned of problems with CCRI's operations, "brought in the best" team of outside experts, and "implemented full and exceptional changes" to bring CCRI into compliance with FDA's clinical research regulations. Ziering April 28, 2003 Letter at 28, 32, and 33.

II. DECISION

² Dr. Ziering states that "[i]t is not my intention to comment on each of Dr. Startzman's accusations. I will if asked—perhaps at a requested Hearing." Ziering April 28, 2003 Letter at 28.

My decision regarding whether the disqualification of a clinical investigator is appropriate is governed by 21 C.F.R. § 312.70(b), which 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.

21 C.F.R. § 312.70(b). Therefore, 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 applicable FDA regulations or repeatedly or deliberately submitted false information to FDA or to the sponsor.

The term “repeatedly,” as it is used in 21 C.F.R. § 312.70(b), is given its plain meaning, such that a clinical investigator may be found to have acted “repeatedly” if he or she engages in proscribed conduct “more than once.” See 13 Oxford English Dictionary 635 (2d ed. 1989) (defining repeatedly as “more than once, again and again, frequently”). In interpreting 21 C.F.R. § 312.70(b), FDA has found that violations of a regulation may occur “repeatedly” when they occur in only one study. See, e.g., Commissioner’s Decision, Regulatory Hearing on the Proposal to Disqualify James A. Halikas, M.D. (2001), at 23 (“[T]o interpret repeatedly to mean transgressions in more than one study would permit an investigator to commit as many violations of the regulations as he/she wished without possibility of disqualification as long as that investigator limited his/her violations to one study. Such a result . . . would be absurd.”). Thus, disqualification may be appropriate after a finding of repeated violative conduct in just one study.

A clinical investigator may be found to have acted “deliberately,” within the meaning of 21 C.F.R. § 312.70(b), if he or she knowingly or willfully engaged in conduct that violates FDA’s regulations or if the investigator engaged in conduct that demonstrated a reckless disregard for compliance with FDA’s regulations. See Safeco Ins. Co. of America v. Burr, — U.S. —, 127 S. Ct. 2201, 2208-2209 (June 4, 2007) (“[W]here willfulness is a statutory condition of civil liability, we have generally taken it to cover not only knowing violations of a standard, but reckless ones as well. This construction reflects common law usage, which treated actions in ‘reckless disregard’ of the law as ‘willful’ violations.”) (citations omitted); see also Farmer v. Brennan, 511 U.S. 825, 836 (1994) (“[T]he Courts of Appeals have routinely equated deliberate indifference with recklessness.”). Thus, a clinical investigator may be found to have acted “deliberately,” even in the absence of proof that the he or she acted knowingly or with a specific intent to violate FDA’s regulations. See Commissioner’s Decision, Regulatory Hearing on the Proposal to Disqualify Hubert M. Vriesendorp, M.D. (2001), § III.C. (“[A]n 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.”); see also United States v. Chestnut, 533 F.2d 40, 48 (2d Cir. 1976) (“Recognizing the inherent difficulty in establishing a willful violation of the law by direct evidence, the Supreme Court has held that willfulness may be inferred from the ‘handling of one’s affairs’ . . . and from ‘conduct’”) (quoting Spies v. United States, 317 U.S. 492, 499 (1943)).

In this administrative proceeding, Dr. Ziering is charged with repeatedly or deliberately failing to comply with 21 C.F.R. Part 312. I will separately address the two charges upon which Dr. Startzman granted summary decision in favor of CDER. I will also consider the three general

objections to disqualification raised by Dr. Ziering. However, as neither CDER nor Dr. Ziering has requested that I review Dr. Startzman's determination with respect to Charges 1 and 4, I will not do so.

A. Charge 2 - Failure to Maintain Adequate and Accurate Case Histories

CDER charged that Dr. Ziering failed to maintain adequate and accurate case histories, in violation of 21 C.F.R. § 312.62(b). That regulation provides:

(b) *Case histories.* An investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

In support of this charge, CDER alleged that Dr. Ziering: (1) submitted machine-generated records from subjects in three separate studies that contained handwritten changes that were not accompanied by documented explanations as to the basis for the corrections; and (2) submitted numerous documents in four studies that contained his forged signature.

1. Unexplained Manual Alteration of Machine-Generated Records

CDER provided machine-generated records from multiple subjects in three studies, Glaxo [] Glaxo [] and [] that contain handwritten changes that are not accompanied by documented explanations as to the basis for the corrections. CDER alleges that these changes were made by CCRI personnel in order to permit patients to participate in the studies who would not otherwise have been eligible for enrollment.

In response to CDER's charge, Dr. Ziering states that he "does not have specific information about who, why, or when these results were recorded," but that he "can present a logical explanation for any discrepancies" reflected in the machine-generated records based on his "understanding of the medical instrumentation used by CCRI's staff to record this patient information." Ziering Sept. 8, 1999 Letter at 11. Dr. Ziering describes various situations in which manual corrections to data could have been required, including where a patient's demographic data was initially entered incorrectly or a staff member failed to reset a machine before running a test on a subsequent patient. Id. at 11-13. Dr. Ziering does not dispute, however, that when the records bearing handwritten changes were submitted to the sponsors, they were not accompanied by documented explanations as to the basis for the manual corrections.

In his Summary Decision, Dr. Startzman held that there was no genuine issue of fact for a hearing on Charge 2 in that Dr. Ziering repeatedly and deliberately violated 21 C.F.R. § 312.62(b) by submitting manually altered records without documented explanations for the changes. Dr. Startzman found that Dr. Ziering's conduct was a violation of the requirements of 21 C.F.R. § 312.62(b) "to prepare and maintain adequate and accurate case histories" because "even if his 'logical explanation' correctly diagnosed the reasons for inaccurate and inadequate records, the fact remains that the records are inaccurate and inadequate because the handwritten changes are not documented as correct." Summary Decision at 34. Dr. Ziering's violations of the regulation were repeated, Dr. Startzman concluded, because "there were more than one." Id. at 43. Finally, Dr. Startzman found that Dr. Ziering's actions were deliberate because he "took so little care with respect to his supervisory duties that he showed reckless disregard for the

possibility that a regulatory violation would result.” Id. As evidence of this reckless disregard, Dr. Startzman found that Dr. Ziering’s “supervisory responsibility includes taking appropriate measures to ensure that violations do not occur,” but that “there was no evidence that Dr. Ziering instructed his staff in proper procedures for correcting machine errors. Nor is there evidence that he took timely steps necessary to determine whether the equipment was malfunctioning, to train his staff in their proper use, or to obtain better equipment.” Id. at 35, 44.

After reviewing the administrative record, I affirm Dr. Startzman’s findings on Charge 2 that there were no genuine issues of fact for a hearing on whether Dr. Ziering repeatedly and deliberately violated 21 C.F.R. § 312.62(b) with respect to the manually altered records. The record is clear that Dr. Ziering submitted machine-generated records that contain handwritten changes that are not accompanied by documented explanations as to the basis for the corrections, and that these violations occurred repeatedly in the Glaxo [] Glaxo [] and [] studies. CDER provided evidence that at least 26 machine-generated records that were manually altered so that the demographics of the patient and/or the time period that the test was conducted would comply with the protocol restrictions for the study being conducted. Among these violations was one subject in the Glaxo [] study who was identified for the first three weeks of the study as being 63 years old, 184 pounds, 72 inches tall, and male. See CDER Motion for Summary Decision at 10, Ex. 15. Then, in the fourth week of the study, the subject was identified as being 49 years old, 112 pounds, 60 inches tall, and female. It was not until over a month later that the gender for this record was changed to male.

The record also supports Dr. Startzman’s determination that Dr. Ziering acted deliberately. As a clinical investigator, Dr. Ziering is required to comply with 21 C.F.R. §

312.62(b), which states that “[t]he investigator is required to prepare and maintain adequate and accurate case histories” (Emphasis added.) Dr. Ziering maintains that he did not know that the records had been manually altered and that, “[a]s the principal investigator, he relied on the professional staff to be knowledgeable about protocol requirements, review clinical charts for protocol issues, and to inform him of any problems.” Ziering Sept. 8, 1999 Letter at 14.

However, the regulation at issue places the ultimate responsibility for ensuring that the records prepared and maintained in a study are adequate and accurate squarely on the shoulders of the clinical investigator. See 21 C.F.R. § 312.62(b). Thus, because Dr. Ziering elected to rely on his staff to prepare and review the records, he was required to supervise them to the extent necessary to ensure that the records they prepared and maintained were adequate and accurate. That CDER identified numerous patient records in three different studies that were neither adequate nor accurate demonstrates that Dr. Ziering grossly neglected his supervisory responsibilities as a clinical investigator. I therefore concur in Dr. Startzman’s ruling that Dr. Ziering deliberately violated 21 C.F.R. § 312.62(b) in that he “took so little care with respect to his supervisory duties that he showed reckless disregard for the possibility that a regulatory violation would result.” Summary Decision at 34; see also Farmer, 511 U.S. at 836 (equating “deliberate indifference with recklessness”).

In summary, I find that there is no genuine and substantial issue of fact that Dr. Ziering violated 21 C.F.R. § 312.62(b) by failing to maintain adequate and accurate case histories when he submitted manually altered, machine-generated records to the sponsors, and I affirm Dr. Startzman’s finding that these violations by Dr. Ziering were repeated and deliberate.

2. Dr. Ziering's Forged Signature on Forms Submitted to the Sponsors

In further support of its charge that Dr. Ziering failed to maintain adequate and accurate case histories, CDER offers numerous forms from five of the studies at issue, including informed consent forms, case report forms, source documents, laboratory reports, and Statement of Investigator forms ("Form FDA-1572"), that were submitted to the sponsors bearing signatures that purport to be that of Dr. Ziering but were not Dr. Ziering's authentic signature. See CDER Motion for Summary Decision at 15 (arguing that "[t]hese falsifications alone prove that Dr. Ziering failed to prepare and maintain adequate and accurate records . . . in violation of 21 C.F.R. § 312.62(b)"); see also 21 C.F.R. § 312.53(c)(1) (requiring a sponsor to obtain a signed Form FDA-1572 from each clinical investigator before the initiation of a study).

As evidence in support of its contention that Dr. Ziering's violations were deliberate, CDER argues that Dr. Ziering was "an experienced clinical investigator with twenty-one (21) studies on record with FDA," and "[a]s an experienced clinical investigator, he would be well aware of the requirement to sign a Form FDA-1572 for each study he performs." CDER Motion for Summary Decision at 15 ("Similarly, he would be well aware that the clinical investigator must sign the [case report forms]."). CDER maintains that "[t]he fact that Dr. Ziering's staff falsified numerous signatures on documents submitted to both FDA and the study sponsors shows that such falsification was both tolerated and accepted behavior" by Dr. Ziering, which demonstrates "a reckless disregard for the requirements of 21 C.F.R. § 312.62(b)." Id. at 15, 16.

Responding to CDER's charge that he submitted documents to the sponsors that contained forged signatures, Dr. Ziering does not dispute that a number of study records do not bear his authentic signature. He insists, however, that he "did not authorize or encourage these

forgeries.” Ziering Sept. 8, 1999 Letter at 13. He further offers that “CCRI has implemented several procedures to ensure that signature documentation problems do not reoccur at the facility.” Id.

In his Summary Decision, Dr. Startzman held that there were no genuine issues of fact for a hearing on whether Dr. Ziering repeatedly and deliberately violated 21 C.F.R. § 312.62(b) in submitting records containing forged signatures. Dr. Startzman found that with respect to the forged signatures, Dr. Ziering “admits that his staff signed his name many times without authorization” and that by definition, a “case history document that has an unauthorized signature is neither ‘adequate’ nor ‘accurate.’” Summary Decision at 42. Dr. Ziering’s violations of the regulation were repeated, Dr. Startzman concluded, because “all but one of the Forms FDA-1572, nearly 100 percent of the [case report] and informed consent forms bore unauthorized signatures.” Id. at 44. Dr. Startzman found that Dr. Ziering’s violations were deliberate because he could not have been “unaware of the unauthorized signatures in view of the very few Forms 1572 and case history documents that were presented to him for his signature.” Id. Dr. Startzman therefore issued a summary decision in favor of CDER on Charge 2.

In his April 28, 2003 letter requesting that I review Dr. Startzman’s summary decision in favor of CDER on this charge, Dr. Ziering contends that he “did sign the [forms], followed the protocols, and returned the signed documents and case report forms to the staff. Then unbeknownst” to him, his staff “perpetrated their criminal acts—including forgeries, altering source documents, burying records, destroying pages of clinical charts, etc.” Ziering April 28, 2003 Letter at 38. This is the first time that Dr. Ziering has raised this argument in this

proceeding, and he provides no evidentiary support for his claim or possible rationale as to why his staff would substitute forged records for genuine ones.

After reviewing the administrative record, I affirm Dr. Startzman's findings on Charge 2 that there were no genuine issues of fact for a hearing on whether Dr. Ziering repeatedly and deliberately violated 21 C.F.R. § 312.62(b) in submitting documents bearing forged signatures to the study sponsors. Dr. Ziering admits that numerous documents containing his forged signature were submitted to the sponsors, and case history documents bearing forged signatures are neither "adequate" nor "accurate." I therefore concur in Dr. Startzman's finding that Dr. Ziering violated 21 C.F.R. § 312.62(b) and did so repeatedly.

The evidence proffered by CDER further supports a finding that Dr. Ziering's violations of 21 C.F.R. § 312.62(b) were deliberate within the meaning of 21 C.F.R. § 312.70(b). CDER points to 21 C.F.R. § 312.53(c)(1), which requires that a clinical investigator sign a Form FDA-1572 before the initiation of each study conducted. As a clinical investigator, Dr. Ziering can be expected to be familiar with this regulation. The evidence provided by CDER, that Dr. Ziering was an experienced clinical investigator who had conducted 21 previous studies, further supports the inference that Dr. Ziering was well aware of his obligation to sign and submit a Form 1572 for each study. For the six studies at issue in this proceeding, however, Dr. Ziering signed only one Form FDA-1572. Even if Dr. Ziering's signature was signed by his staff without his knowledge, his failure to investigate further when the Form FDA-1572s for the other five studies were not presented for his signature demonstrates a reckless disregard for compliance with the FDA regulations governing clinical investigations.

Similarly, as a veteran clinical investigator, Dr. Ziering would have been aware that 21 C.F.R. § 312.62(b) requires the clinical investigator sign the case report forms. The fact that “nearly 100 percent” of the case report forms bore unauthorized signatures demonstrates a reckless disregard for compliance with the FDA regulations governing clinical investigations. Summary Decision at 42. I therefore conclude that there is no genuine and substantial issue of fact that Dr. Ziering deliberately violated 21 C.F.R. § 312.62(b) through his submission of records containing forged signatures.

B. Charge 3 - Failure to Follow the Investigational Plan

CDER charged that Dr. Ziering failed to follow the investigational plan, in violation of 21 C.F.R. § 312.60. That regulation provides that “[a]n investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations” In support of this charge, CDER provides documentation of deviations from protocols for chest x-rays, pulmonary function tests, and blood samples for subjects enrolled in three of the studies at issue in this proceeding: Glaxo [] Glaxo [] and []

The protocol for Glaxo [] and [] required patients in the studies to have chest x-rays on their first visits if they had not had a negative chest x-ray in the previous 12 months. CDER provided evidence that with respect to four patients, there was no evidence that any chest x-rays had ever been taken. With respect to another ten patients, CDER’s evidence demonstrated that the required x-rays were not taken until after the first visit.

In addition, the protocol for Glaxo [] required a post-dosing pulmonary function test be performed on patients 15 minutes after the pre-dosing pulmonary function test. CDER provided evidence that one patient did not receive this test until two hours after the pre-dosing test. Similarly, the protocol for Glaxo [] required a 30-minute interval between pre- and post-dosing pulmonary function tests. CDER provided evidence that these post-dosing tests were twice performed only 12 minutes after the pre-dosing test. Finally, the protocol for [] required a blood sample to be drawn and a pre-dose electrocardiogram be performed on a patient's fifth visit. CDER contends that with respect to one patient in the study, no records exist to show that either test was ever conducted.

In response to CDER's allegations, Dr. Ziering once again offers a "logical explanation" for the discrepancies, but states that he cannot offer specific evidence regarding the records in these studies because he delegated the patient procedures to his professional staff, whom he relied upon "to be knowledgeable about protocol requirements, review clinical charts for protocol issues, and to inform him of any problems." See Ziering Sept. 8, 1999 Letter at 14.

In his Summary Decision, Dr. Startzman found that there were no genuine issues of material fact for a hearing on Charge 3 and that Dr. Ziering both repeatedly and deliberately violated 21 C.F.R. § 312.60 by failing to follow the investigative plans for the three study protocols. Specifically, Dr. Startzman determined that Dr. Ziering did not dispute CDER's evidence with respect to each of the specific deviations from the protocols, but blamed his staff for the discrepancies. Dr. Startzman found that it was Dr. Ziering's responsibility as the clinical investigator to ensure that the protocols for the studies were followed. See 21 C.F.R. § 312.60

("An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement [and] the investigational plan.").

After reviewing the administrative record, I find that Dr. Startzman's conclusion that there is no genuine issue of fact that Dr. Ziering repeatedly and deliberately violated 21 C.F.R. § 312.60 is appropriate, and I affirm it. Dr. Ziering does not dispute CDER's evidence that the protocols were not followed in three of the studies at issue in this proceeding, which establishes that Dr. Ziering repeatedly violated 21 C.F.R. § 312.60. Moreover, contrary to Dr. Ziering's assertion that it was appropriate for him to rely upon his staff to perform these procedures in conformance with the study protocols, it remains an investigator's responsibility to ensure compliance with the investigational plan for a study. See 21 C.F.R. § 312.60. The fact that Dr. Ziering's supervision of his staff was so lax as to permit them to deviate from protocols in their dealings with numerous patients enrolled in three different studies demonstrates a reckless disregard on the part of Dr. Ziering to follow the investigational plan. From this reckless conduct it can be inferred that Dr. Ziering's violations of 21 C.F.R. § 312.60 were deliberate. See Safeco Ins. Co. of America, 127 S. Ct. at 2208 ("[W]here willfulness is a statutory condition of civil liability, we have generally taken it to cover not only knowing violations of a standard, but reckless ones as well.").

Even if the evidence proffered by CDER were not sufficient to support a finding that Dr. Ziering acted deliberately in failing to follow the investigational plan, in violation of 21 C.F.R. § 312.60, there is additional evidence available to me that further supports this finding: Dr. Ziering's plea agreement in the criminal prosecution that stemmed from the conduct at issue in this disqualification proceeding. See Memorandum of Plea Agreement Pursuant to Rule

11(e)(1)(B) of the Federal Rules of Criminal Procedure, Crim. No. 00-5212, (E.D. Cal. Jan. 11, 2002) (“Ziering Plea Memo”). Dr. Ziering’s plea agreement was entered after the parties had already submitted their briefing in this matter to Dr. Startzman. See Summary Decision at 19 (referencing Dr. Ziering’s motion to suspend this disqualification proceeding during the pendency of his criminal action). Accordingly, I will take judicial notice of Dr. Ziering’s plea agreement. See 21 C.F.R. § 16.26 (“[T]he presiding officer may issue a summary decision on any issue in the hearing if the presiding officer determines from the 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.”) (emphasis added); Fed. R. Evid. 201(b) (“A judicially noticed fact must be one not subject to reasonable dispute in that it is . . . capable of accurate and ready determination by resort to sources whose accuracy cannot reasonably be questioned.”).

Dr. Ziering was charged with fourteen counts of aiding and abetting mail fraud, in violation of 18 U.S.C. §§ 2 and 1341, six counts of which were related to fraud in his conduct of clinical research trials. Through the agreement he reached with the government, Dr. Ziering pled guilty to one count of aiding and abetting mail fraud in connection with the[

]study that is also at issue in this proceeding.³ Ziering Plea Memo at ¶ 3(p). As part of the plea agreement, Dr. Ziering received a reduction in his recommended prison sentence “due to his acceptance of responsibility” for “a material deviation from the protocol” in the

³ Though not dispositive in the present proceeding, it bears noting that in his plea agreement, Dr. Ziering also agreed “never to receive investigational drugs, animal drugs, biologics, devices or food additives, [or] participate in any manner in the conduct of any further studies, intended or required for submission to the FDA, of investigational products regulated by

[] study. Id. Specifically, Dr. Ziering admitted that he had sent a letter to [] verifying that he had personally examined study subjects as required by the protocol . . . [, h]owever, defendant Ziering knew at the time that he sent the January 18, 1995 letter to [] . . . that, in fact, he had not actually examined all of the research subjects.” Id.

The plea agreement from Dr. Ziering’s criminal prosecution conclusively establishes for the purposes of this proceeding that he knowingly failed to follow the study protocol for the [] study. See also United States v. Perez-Corona, 295 F.3d 996, 1001 (9th Cir. 2002) (observing that it is appropriate to “take judicial notice of the underlying facts” contained in a “court document, such as an information or indictment, a signed plea agreement, jury instructions, the transcript of a plea hearing, or the judgment of conviction”). Therefore, I find that there are no genuine issues of material fact for a hearing on Charge 3 in that Dr. Ziering both repeatedly and deliberately failed to follow the investigative plans of the studies he conducted, in violation of 21 C.F.R. § 312.60.

C. Dr. Ziering’s Remaining Objections to Disqualification

1. Were Relevant Records Available to Dr. Startzman

As noted earlier, in addition to contesting several factual issues concerning the charges as discussed above, Dr. Ziering impliedly requests that I review the Summary Decision on several additional grounds. First, Dr. Ziering asserts that “Dr. Startzman was handicapped in the dearth of materials at his disposal” in reaching the summary decision. Ziering April 28, 2003 Letter at FDA.” Ziering Plea Memo at ¶ 3(g).

28. Specifically, Dr. Ziering states that “[m]ainly I see [that Dr. Startzman] reviewed the Government’s highly skewed documents and the 483 EIR. My perception is Dr. Startzman was handicapped in the dearth of materials at his disposal.” Id. Dr. Ziering does not, however, list any specific materials that he contends were relevant to the disqualification determination but not made available to Dr. Startzman.

Elsewhere in his letter requesting my review of the Summary Decision, Dr. Ziering voices his “regret that [he] do[es] not have the case record available to [him]” as he is “now in forced retirement, living in a distant city, and you have offered limited time for a rebuttal.” Id. at 47. He also states that from the related civil and criminal proceedings in this matter, “[t]here are tons of boxes of records of proceedings,” but that he has “been able to secure but a portion of these, piece by piece—through depositions, trials, and the indictment.”⁴ Id. at 3. Though he implies that these documents support his position that disqualification is inappropriate, he does not describe or identify particular documents that he contends were relevant to the disqualification question that were not provided to Dr. Startzman.

In any event, the responsibility was on Dr. Ziering to include in the record any evidence he deemed necessary for presenting his defense. See, e.g., Holy Cross Wilderness Fund v. Madigan, 960 F.2d 1515, 1528 n.18 (10th Cir. 1992) (“[W]e will not review information that a

⁴ Though he does not provide any details regarding these other legal proceedings, at various points in his April 28, 2003 submission, Dr. Ziering references his criminal prosecution as well as the civil awards and/or settlements allegedly obtained by members of his former staff who had accused him sexual harassment.

party failed to include in the administrative record or present before the agency.”) (citation and quotation marks omitted). 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) (affirming the district court’s grant of summary judgment where the party resisting such a ruling relied upon only the allegations in its pleadings). Indeed, the Summary Decision reflects that Dr. Startzman carefully considered all materials provided to him by the parties. See Summary Decision at 1. Based upon my review of the record, I find that Dr. Startzman appropriately considered and relied upon all relevant evidence that was provided to him by the parties in this proceeding.

2. Is Dr. Ziering Responsible for the Violative Actions of His Staff

Dr. Ziering also requests that I review the Summary Decision in light of his view that the standard that “the Principal Investigator is ‘ultimately responsible’ . . . must be interpreted in the context of the intent” of the investigator. Ziering April 28, 2003 Letter at 32. Dr. Ziering presents this argument slightly differently elsewhere in his submission when he states that “[h]owever true [the maxim that] the principal investigator is responsible for the activities of his staff,” because Dr. Ziering “was the victim of coordinator fraud” orchestrated by his “trusted research staff,” applying that maxim to him would “carry this to the absurd.” Id. at 4-5, 55; see also id. at 48 (“Are we all to anticipate every possible transgression possible from those we deal with? Are we to enumerate all stated possibilities for them to ultimately violate? To believe it an imperative to forewarn a then trusted staff . . . not to forge my name, is pure drivel.”).

The Summary Decision reflects that Dr. Startzman considered “Dr. Ziering’s position . . . that the investigator is not responsible if violative activities are not preformed by him, or

undertaken at his direction.” Summary Decision at 13. In ruling in favor of CDER, Dr.

Startzman found

that Dr. Ziering had assumed responsibility for proper execution of the studies conducted at his site when he agreed to be principal investigator for the clinical trials. Regulation 21 C.F.R. § 312.60 states that an investigator ‘is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations.’

Summary Decision at 14. In addition, Dr. Startzman observed that “Dr. Ziering admitted that he was responsible for ensuring compliance with the protocols.” Id. at 52.

In evaluating Dr. Ziering’s argument on this point, I find that his contentions are actually an implied attack on Dr. Startzman’s finding that Dr. Ziering acted deliberately. In effect, Dr. Ziering argues that because he was unaware of the violative actions taken by his staff, any violations were not “deliberately” undertaken by him. See Ziering April 28, 2003 Letter at 8 (directing my attention to the fact that there is “no proof” that his staff informed him of their allegedly violative activities).

For the reasons that I discussed above in setting forth the “deliberately” standard that applies to decisions under 21 C.F.R. § 312.70(b), I find the argument advanced by Dr. Ziering is without merit. Dr. Ziering’s actions in neglecting to maintain adequate and accurate case histories and failing to follow the investigational plans for the studies he conducted demonstrate a reckless disregard for the requirements of 21 C.F.R. § 312.70(b). A clinical investigator may be found to have acted “deliberately” even in the absence of proof that the he or she acted knowingly or with a specific intent to violate FDA’s regulations if the investigator’s actions show a reckless disregard for whether a violation could occur. Thus, based upon my review of

the record, I agree with Dr. Startzman that Dr. Ziering deliberately violated the regulations governing clinical investigators and affirm Dr. Startzman's finding on these charges.

3. Is it Relevant Whether Dr. Ziering Has Implemented Corrections to Assure Future Compliance

Finally, Dr. Ziering requests that I review the Summary Decision on the grounds that disqualification is inappropriate in light of the fact that he investigated as soon as he learned of problems with CCRI's operations, "brought in the best" team of outside experts, and "implemented full and exceptional changes" to bring CCRI into compliance with FDA's clinical research regulations. Ziering April 28, 2003 Letter at 33, 31. Dr. Ziering states that when he became "[d]isillusioned by staff and monitors alike, [he] decided to become more personally knowledgeable . . . [and] become a coordinator [him]self . . . , [by] tak[ing] the certifying examination" for clinical research coordinators. *Id.* at 25-26. According to Dr. Ziering, he "took and passed the coordinator exam given April, 1995." *Id.* at 26.

In his Summary Decision, Dr. Startzman considered this argument and found that "the corrections Dr. Ziering allegedly made are irrelevant to the factual findings that I must make. This is clear from the final regulations concerning disqualification of clinical investigators of new drugs." Summary Decision at 53. Dr. Startzman further observed that Dr. Ziering's "claim that CCRI is now in compliance with regulations" was "uncorroborated and his changes have not been implemented in ongoing studies." *Id.*

The investigational drug regulations in 21 C.F.R. Part 312 provide that once a finding is made that an investigator has repeatedly or deliberately failed to comply with the applicable requirements, disqualification generally must follow. *See* 21 C.F.R. § 312.70. The regulations

provide little discretion for alternative resolution and do not suggest that remedial corrections relieve an investigator of disqualification on the basis of previous violations. In the preamble to 21 C.F.R. § 312.70, FDA rejected the option of lesser sanctions, providing instead that disqualification would be the general response to violations. See 52 Fed. Reg. 8798, 8826 (March 19, 1987). The preamble does provide the Commissioner with limited discretion to not disqualify an investigator if the Commissioner believes that the investigator's violations are insignificant or lesser sanctions would be adequate, but the preamble makes clear that this discretion may be exercised only in extraordinary circumstances. See Commissioner's Decision, Regulatory Hearing on the Proposal to Disqualify James A. Halikas, M.D. (2001), at 28 (offering as examples of extraordinary circumstances "where the violations are truly insignificant, or where disqualification would be truly unjust or would accomplish nothing").

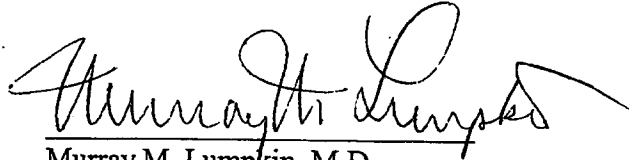
Given the findings in this matter, such extraordinary circumstances do not exist. I find that Dr. Ziering repeatedly and deliberately violated the regulations requiring him to keep adequate and accurate case histories and failed to follow the investigational plan for the studies he conducted at CCRI. I find that these violations are sufficiently serious and numerous so as to require disqualification.

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. Ziering failed to fulfill the responsibilities of an investigator, in violation of 21 C.F.R. Part 312. Under 21 C.F.R. § 312.70, my findings on Charges 2 and 3 are sufficient to disqualify Dr. Ziering.

IV. CONCLUSION

I therefore conclude that Dr. Ziering is no longer eligible to receive investigational drugs.
Dr. Ziering may seek to have his eligibility to receive investigational drugs reinstated pursuant to
21 C.F.R. §_312.70(f).



Murray M. Lumpkin, M.D.
Deputy Commissioner
International and Special Programs

Dated: May 20, 2008